SYNTHETIC STUDIES DIRECTED TOWARDS UNDERSTANDING FACIAL SELECTION IN DIELS-ALDER REACTIONS

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Contents

Abstract

Chapter 1 of this thesis briefly introduces the Diels-Alder reaction and highlights the stereochemical aspects of the reaction including *endo* versus *exo* addition, regioselectivity and π-facial selectivity. Some examples of systematic studies of π-facial selectivities are given.

In Chapter 2 the syntheses, incidental chemistry and Diels-Alder reactions of two monosubstituted cage-fused dienes, the monoethylene acetal **52** and monothioethylene acetal **53** are described. With alkene dienophiles, the cycloaddition reactions gave almost exclusively "bottom face" adducts, while acetylenic and azo dienophiles gave mixed selectivities. An X-ray determined crystal structure of the monoethylene acetal-nitrosobenzene adduct **99** is reported. Reactions of the cage diketone **35** with various alcohols and a crystallographic study of the diisopropoxyacetal **65** are also reported.

Syntheses and Diels-Alder reactions of two symmetrically modified cage dienes, the dialkane **103** and dioxime **104**, are described in Chapter 3. X-ray crystal structures of the dialkane-dimethyl acetylenedicarboxylate **117** and dioxime-N-phenyltriazoline dione **119** adducts are reported. The latter study revealed the oxime moieties are oriented anti to the cyclobutane ring. Diels-Alder reactions of dialkane **103** gave exclusively "bottom face" adducts showing that, in the absence of unfavourable electronic effects, the "bottom face" is sterically favoured. The dioxime **104** gave mixed selectivities.

In Chapter 4 syntheses of cage ether **121**, cyclic acetal **122** and amide **140**, incidental chemistry of the cage compounds and their Diels-Alder reactions are reported. With the alkene dienophiles preference for "bottom face" attack was observed. The reactions of ether **121** and cyclic acetal **122** with acetylenic and azo dienophiles showed a high preference for the "top face". This is attributed to "closed shell repulsion".

Diels-Alder reactions of hydroxyketone **143** and the acetate **144** are described in Chapter 5. These reactions gave only "bottom face" adducts. Thus, hydrogen bonding interactions as a determining factor in π-facial selectivities is ruled out.

Molecular mechanics modelling of the adducts and diastereomeric "transition state" (TS) structures were undertaken to rationalise the observed π-facial selectivities. Product stabilities were shown to be unimportant. A model based on steric and torsional effects at the TS can qualitatively predict the π-facial selectivities for reactions of all the dienes with alkene dienophiles. With acetylenic dienophiles the TS model predicted a high preference for the "bottom face". This prediction was in agreement with experiment only for the dialkane-DMAD adduct. An alternative new explanation is given for these reactions involving through-space filled orbital repulsive interactions between the diene substituents and the orbitals of the dienophile which are orthogonal to the bond forming HOMO π orbitals.

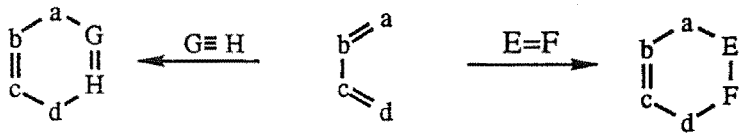
Chapter 1

Introduction

1.1 General

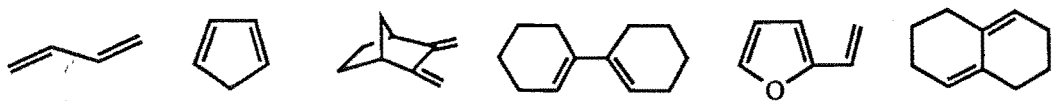
The Diels-Alder reaction[1] is one of the most useful reactions in synthetic organic chemistry and is widely used for forming carbon-carbon, carbon-heteroatom and heteroatom-heteroatom bonds.[2,3,4,5] It is a [π4 + π2] cycloaddition involving a 1,3-diene component and another component, called a dienophile, to form a 6-membered ring product [**Scheme 1.1**].

Scheme 1.1



In the reaction, two new σ-bonds are formed at the expense of two π-bonds in the starting materials. The cycloaddition may be intermolecular or intramolecular.[6,7]

In general, the reaction takes place quite easily at room temperature but with less reactive dienes and dienophiles more vigorous conditions such as heating in a suitable solvent may be required. The cycloaddition reaction is reversible and the reverse process is called a retro Diels-Alder reaction. Many adducts dissociate into their components at quite low temperature, in particular those formed from cyclic dienes such as cyclopentadiene, fulvene or furan.



1 **2** **3** **4** **5** **6**

The diene is the 4π component of the Diels-Alder reaction and may be classified as open-chain (e.g. **1**), endocyclic (e.g. **2**), exocyclic (e.g. **3**), inter-ring (e.g. **4**) or extra-intra-ring (e.g. **5**), with the condition that it may not be constrained to a transoid conformation. If it is held in the transoid conformation (e.g. **6**), the reaction does not take place. The diene either must be held in the cisoid conformation or must be able to

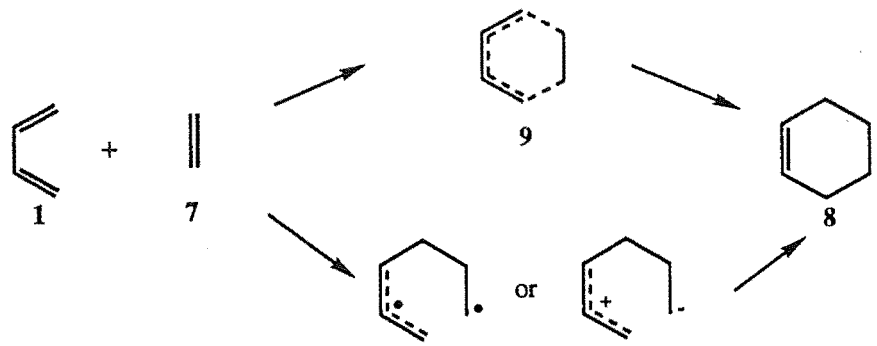
achieve it during the reaction.[8] This condition is crucial in order to obtain overlap between the π-orbitals in the diene and dienophile.

The 2π component in the Diels-Alder reaction, the dienophile, is more varied. It may be a derivative of ethylene or acetylene or a reagent in which one or both the reacting atoms is a heteroatom. Carbon-carbon double or triple bonds are activated in a "normal demand" reaction (i.e. one involving a conjugated or electron-rich diene and an electron deficient dienophile) by electron-withdrawing substituents. A strong increase in reactivity is observed by introducing more than one electron-withdrawing group as has been shown in the kinetic study on the reactions of cyclopentadiene with cyanoethenes.[9]

1.2 Mechanism of the Diels-Alder reaction

The Diels-Alder reaction is bimolecular and the two components approach each other in parallel planes roughly orthogonal to the direction of the new bonds about to be formed. The two new σ-bonds are formed by the overlap of molecular π-orbitals in a manner similar to endwise overlap of atomic p-orbitals.

Scheme 1.2



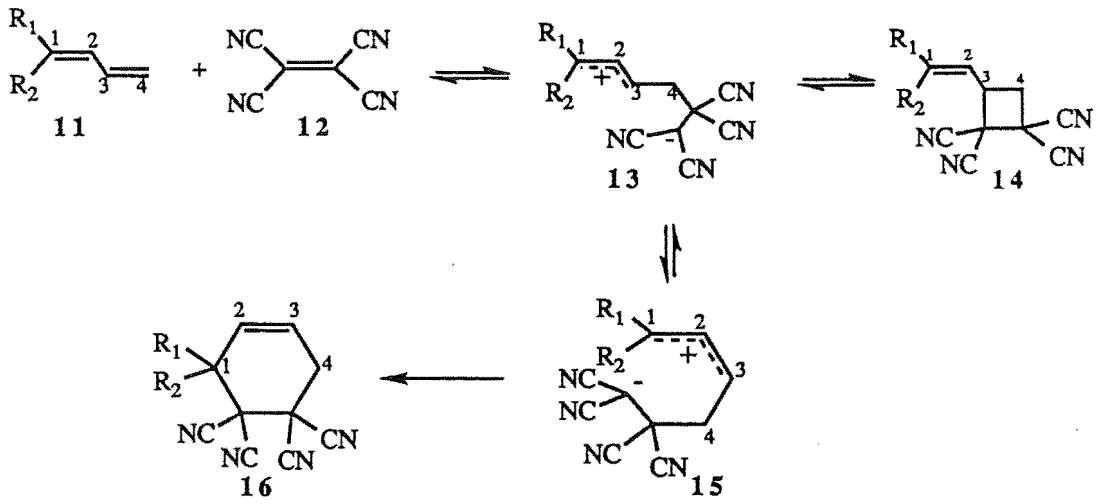
Extensive investigations of the reaction mechanism[10,11,12,13] have shown that all the Diels-Alder cycloadditions cannot be interpreted in terms of one mechanism. There are two main descriptions of the mechanism. In the first, the reaction proceeds through a concerted† and synchronous§ mechanism involving a cyclic aromatic "transition state" (TS) **9**.[14] A concerted but nonsynchronous mechanism in which the TS is unsymmetrical has also been proposed. Alternatively the reaction proceeds by a two-

† A concerted reaction is one that takes place in a single step.
§ A synchronous reaction is a concerted reaction in which the various changes in bonding have progressed to similar extents in the transition state.

step* mechanism, involving an intermediate biradical or zwitterion [**Scheme 1.2**]. In the two-step mechanism, it is assumed that the first step, to form the intermediate **10**, is rate-determining and that the second step to form the product **8** is fast.

There is evidence for both mechanisms. The concerted mechanism is supported by the following: (i) the syn stereospecificity of the reaction. However, a two-step mechanism cannot be ruled out based on this evidence; if the rate of formation of the second bond is much faster than rotation about the single bond in the intermediate **10**, syn stereospecificity would also be observed. (ii) Solvent effects, such as polarity, on the rate of reaction are very small; this would not be expected for a zwitterionic intermediate. (iii) The large negative values of both activation entropy and activation volume give further support to a concerted mechanism with a geometrically highly oriented TS.[15,16] (iv) Investigations of kinetic istope effects[17] on the secondary α-deuterium isotope effects in a retro-Diels-Alder reaction of 9,10-dihydro-9,10-ethanoanthracene and its bridge-deuterated analogues yielded results which are in favour of a concerted mechanism. By the principle of microscopic reversibility, the forward reaction should have the same rate-determining transition state.

Scheme 1.3



There is also evidence for the two step mechanism in some Diels-Alder reactions; for example, the competition between [π2 + π2] and [π4 + π2] cycloadditions of 1,1-disubstituted 1,3-dienes **11** and tetracyanoethene **12** [**Scheme 1.3**].[18] The mechanism in Scheme 1.3 is supported by product analyses and kinetic studies which include the

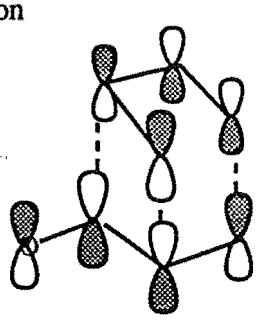
* A two step reaction takes place in two distinct kinetic steps via an intermediate (energy mininum).

dependence of reaction rate on solvents. The kinetically controlled reaction yields the thermodynamically unstable, four-membered ring adduct **14** which then reverses through **13** and **15** to form the more stable cyclohexene derivative **16**, the [π4 + π2] adduct.

While there is general agreement that most thermal cycloadditions can be described by a symmetry-allowed one step mechanism, the timing of the formation of the two bonds (i.e. synchronous versus nonsynchronous formation of the two σ-bonds) is a source of controversy.[12,19,20] Both experimental and theoretical evidence in favour of a concerted synchronous mechanism for the prototype Diels-Alder reaction of 1,3-butadiene **1** with ethene **7** have been reported.[11] On the other hand, Dewar et al. proposed a nonsynchronous mechanism for the reaction of 1,3-butadiene and cyanoethylenes based on semi-empirical calculations on the "transition state" structures of these reactions.[21] However, they maintained that the mechanism for the Diels-Alder reaction of 1,3-butadiene and ethene remained uncertain.[21]

Various aspects of cycloaddition reactions such as reactivity and selectivity have been successfully rationalised by the Woodward and Hoffmann rules[22a] and by Fukui's frontier molecular orbital (FMO) theory.[22b,23] The FMO theory has its origins in Perturbation theory;[24] however in the "frontier orbital" approximation only the most dominant stabilising terms, those arising from the interaction of the highest occupied molecular orbital (HOMO) with the lowest unoccupied molecular orbital (LUMO), are considered. According to the theory, the Diels-Alder reaction is controlled by the "in-phase" interaction of the two HOMO-LUMO molecular orbitals which are closest in energy. In the case of a [π4 + π2] cycloaddition, this is achieved only when the HOMO-LUMO interactions are suprafacial [**Figure 1.1**].

Figure 1.1 HOMO-LUMO orbital arrangement in the *endo* transition state of butadiene-acrolein interaction

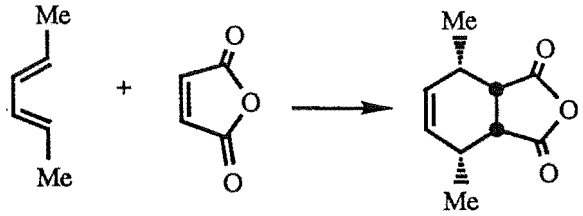


1.3 Regio- and Stereo-chemistry

1.3.1 *Endo-exo-* and regio-selectivity

The fact that the relative configuration of groups in the reactants is preserved in the adducts was first observed by Alder and Stein and from this evolved the "cis principle".[25] For example, the reaction of (E,E)-2,4-hexadiene with maleic anhydride gives an adduct with the methyl groups in the cis configuration [**Scheme 1.4**].

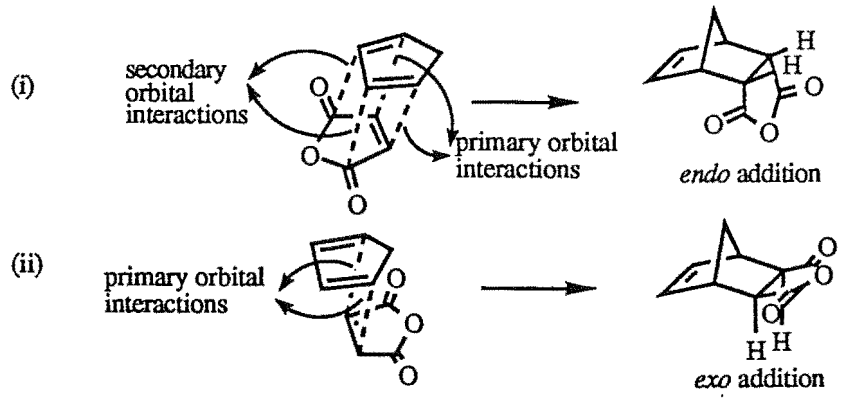
Scheme 1.4



The retention of the relative configuration of the reactant groups in the adduct can be explained by the suprafacial addition of each component. The almost universal observation of the "cis principle" in Diels-Alder reactions in the early days provided strong evidence for the concerted mechanism.

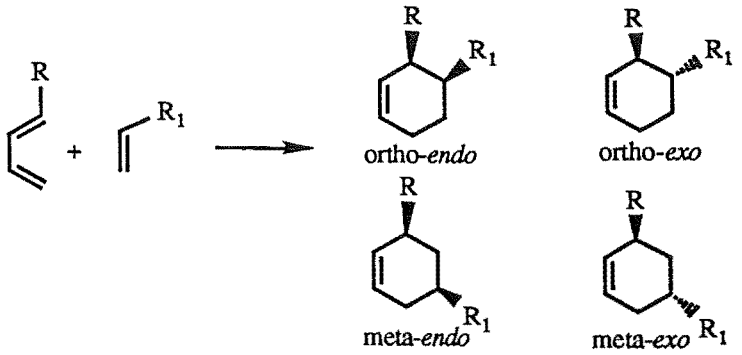
Furthermore, an unsymmetrical dienophile approaching the diene in parallel planes may interact with it in two different orientations: (i) with the bulky sides of the component positioned over each other and (ii) with the bulky side of one component under the smaller side of the other component, leading to the *endo* and *exo* adducts respectively [**Figure 1.2**].

Figure 1.2 *Endo* and *exo* addition for the reaction of maleic anhydride and cyclopentadiene



Furthermore, reaction of an unsymmetrical diene with an unsymmetrical dienophile can give rise to regioisomerism as well as stereoisomerism [**Scheme 1.5**].

Scheme 1.5



The preference for *endo* addition was first rationalised by Alder and Stein in terms of the "maximum accumulation of double bonds".[26] Other explanations for this experimental observation include: secondary orbital interactions,[10,27] inductive[28] or charge-transfer interactions[29] and the geometrical overlap relationship of the π-orbitals at the primary centers.[30] For cyclic dienes and dienophiles, preference for *endo* addition is generally observed when the reaction is under kinetic control. Secondary orbital interactions between atoms which are not bonded in the adduct [**Figure 1.2**] account for the preference for *endo* addition in most cycloadditions.

As shown in Scheme 1.5, cycloadditions involving unsymmetrical dienes and dienophiles can produce structurally isomeric products. In practice, the formation of one of the isomers is strongly favoured. In additions of 1-substituted butadienes, the ortho adducts are favoured while in the case of 2-substituted butadienes, the para adducts predominate. This previously puzzling aspect of the Diels-Alder reaction has been rationalised using frontier molecular orbital theory.[31,32,33]

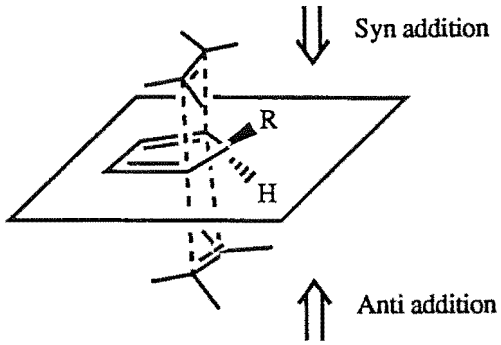
The prevalent use of FMO theory to account for pericyclic reactions has been criticised by Dewar.[34] According to him, FMO theory does not have a good basis in quantum mechanics because it involves a simplifying assumption that the second order pertubation term is dominant, which cannot be justified in many instances. He proposed the use of Pertubation molecular orbital theory instead.[35]

1.3.2 Facial selectivity

Another aspect of the stereochemistry of the Diels-Alder reaction becomes important when the two faces of the π system of the interacting diene and/or dienophile are not equivalent. This phenomenon is observed when the nodal plane of the π bonds in

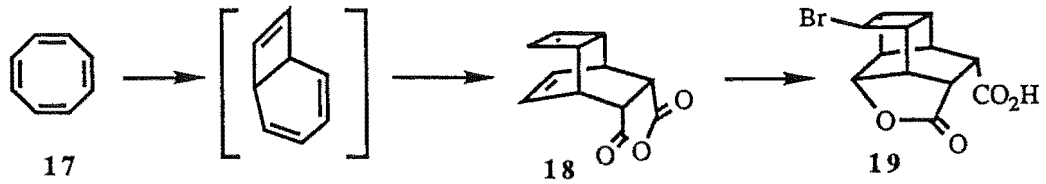
either or both the addends is not a plane of symmetry. In this case, the cycloaddition may give adducts that are diastereoisomers. The two modes of addition are called syn and anti with respect to the group, or structural moiety, that differentiates the two faces [**Figure 1.3**].

Figure 1.3 Syn and anti addition to a monosubstituted cyclopentadiene

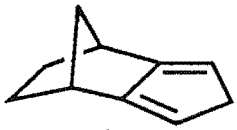


One of the earliest explanations to account for π-facial selectivity was the "steric approach control" principle advocated by Martin and Hill in a review of stereochemistry of the Diels-Alder reaction.[26] In that review, the authors stated that where a choice of π-faces is available, addition should occur from the less hindered face. For example, in the reactions of norbornene, as a dienophile addend, addition occurs from the less hindered methano bridged face to give *exo* adducts. In another example involving an unsymmetrical diene, cyclooctatetraene **17**, which cyclises to bicyclo[4.2.0]octatriene, addition of maleic anhydride occurred from the less hindered face, anti to the cyclobutene moiety, to give the adduct **18** [**Scheme 1.6**].[36] The stereochemistry of the adduct was confirmed by its conversion with bromine to the lactone **19.**

Scheme 1.6



Despite the adherence of many reactions to this rule in the early days, Martin and Hill recognised exceptions to the rule, for example in the reactions of isodicyclopenta-



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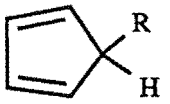


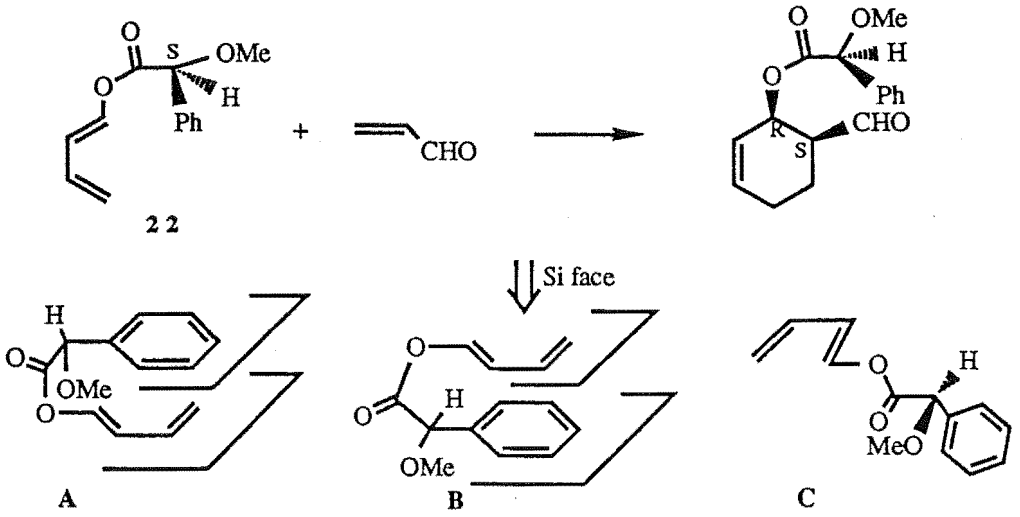
21a R = CO_2Me
21b R = $OCOCH_3$

diene **20**[37] and some monosubstituted cyclopentadienes **21a** and **21b**.[38a,b]

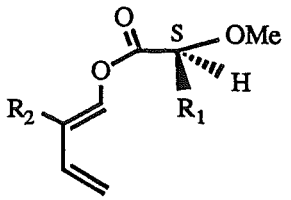
Unlike the other stereochemical aspects of the Diels-Alder reaction, e.g. *endo-exo* and regioselectivity, which had been fairly well accounted for by the FMO theory, π-facial selectivity is much less well understood. The phenomenon appeared to depend on both the diene and dienophile components and has so far eluded generalisation and predictions by any generalised theories. Some examples of studies of this aspect of the Diels-Alder reaction are reported here but this is by no means an exhaustive list as the possible combinations of disymmetric dienes and dienophiles are enormous.

1.3.2.1 Acyclic dienes

Scheme 1.7



Examples of successful investigations into diastereofacial selectivity involving disymmetric acyclic dienes and dienophiles are far fewer than cyclic and fused-cyclic dienes since such investigations are complicated by the conformation flexibility of the components. An example of an investigation of diastereofacial selectivity of an acyclic diene is that of the chiral diene, (S)-1-(O-methylmandeloxy)butadiene **22**, which has been used in asymmetric Diels-Alder synthesis.[39] The high diastereofacial selectivity of acrolein for **22** in the BF_3 catalysed reaction afforded a 82:18 ratio of the two *endo* adducts. The configuration of the major adduct was explained by a π-stacking model. In this model, two possible conformations **A** and **B** are envisaged for the "transition state" structures. **A** shows severe nonbonded interactions and hence the conformer **B** undergoes preferential dienophile addition opposite to the phenyl-shielded diene face, i.e. from the Si-face **[Scheme 1.7]**.[39]

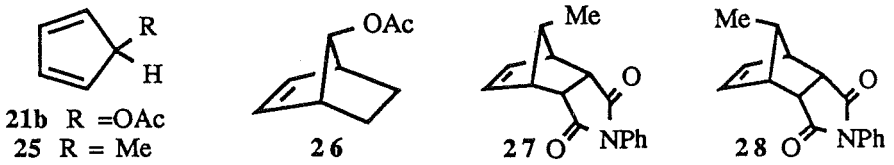


23 $R_1 = C_6H_{11}$, $R_2 = H$
24 $R_1 = C_6H_5$, $R_2 = CH_3$

This TS conformation model of **22** has been questioned by Thornton et al.[40] on the grounds that analogues of **22**, such as **23** and **24** in which π-stacking cannot be invoked, showed the same diastereofacial selectivity. Furthermore, in the reaction of **24**, where TS conformational models **A** and **B** should not be favoured, even higher diastereofacial selectivities are observed. To account for the diastereofacial selectivity of **22**, they proposed a TS model **C** in which the phenyl group is nearly perpendicular to the ester C=O, i.e. the Ph-C-C=O dihedral angle is close to 90° and the methoxy group is close to the carbonyl oxygen. According to Thornton, this orientation of the phenyl group would still block one face of the diene. In support of their proposal were X-ray structure determinations of the adducts of **22** with benzoquinone and naphthoquinone in which the conformations of the phenyl rings (Ph-C-C=O dihedral angles of 99.2° and 95.4°) are in good agreement with their proposed TS model.

1.3.2.2 Cyclic dienes

One of the simplest disymmetric cyclic dienes is the 5-substituted cyclopentadiene 5-acetoxy-1,3-cyclopentadiene **21b** which, contrary to the "steric control approach" enunciated by Martin and Hill,[26] reacted with ethylene to give the anti-product[1] **26**.[38]



21b R =OAc
25 R = Me

26

27

28

Similarly, the 5-methyl derivative **25** reacted with N-phenylmaleimide to give **27** and **28** in a 1:1 ratio.[41] In the early days, before advances made in NMR spectroscopy in the 1960s, the study of syn-anti isomerism was hampered by the difficulty of structure elucidation. Some of the earlier stereochemical assignments have been proved to be incorrect. For example, the previously proposed dimerization of 5-carbomethoxy-1,3-cyclopentadiene to **29**[38b] has been shown to give **30**.[42]

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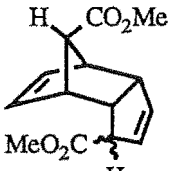
[1] The anti-product here means the adduct with the R substituent on the bridge of the adduct oriented opposite to the alkene bond.



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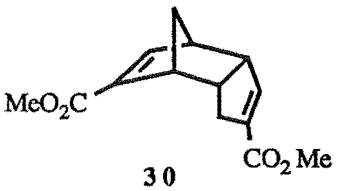

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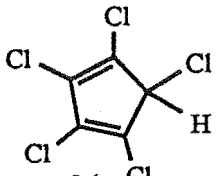
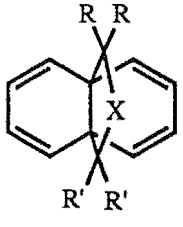


31

One of the earliest systematic studies of π-facial selectivities using a cyclopentadiene substrate was the investigation of the Diels-Alder reactions of 1,2,3,4,5-pentachlorocyclopentadiene **31** by Williamson and co-workers.[43,44] In that study, they noted the preference for the anti-7-chloro isomers in many instances and this preference was increased by catalysis with Lewis acids.[44] They believed two opposing forces governed this syn-anti ratio: steric effects which favour the syn 7-chloro isomer on one hand and a positive attraction between the 7-chloro group and the dienophile which favours the anti 7-chloro isomers on the other. They noticed a correlation between the dipole moments of the monosubstituted dienophile and the percentage of anti 7-chloro isomers and proposed attractive dipole-dipole, dipole-induced dipole and London-dispersion interactions between the dienophile and the polarizable bridge chlorine atom in the TS. In the case of catalysis, complexation of aluminium chloride with the dienophiles such as acrylonitrile would made the dienophile-Lewis acid complex more polar, which would increase the proportion of anti 7-chloro product. The predominance of *endo* over *exo* isomers was explained by secondary orbital interactions.[45] The absence of the anti-*exo* isomers was ascribed to steric hindrance at the transition state.

1.3.2.3 Propellane compounds

A comprehensive study of π-facial selectivity in the propellane type system **32** has been carried out by Ginsburg et al.[46a-g]



32a X = O, R = R' =H
32b X = NCH_3, RR = R'R' = O
32c X =O, RR =O, R' = H
32d(i) X = NPh, RR = R'R' =O
32d(ii) X = N^{t}Bu, RR = R'R' = O
32d(iii) X = N  RR = R'R' =O

In Diels-Alder reactions of propellanes **32**, the dienophile can add syn to the 5-membered ring (i.e. from the "top face" as drawn) or anti to that bridge. Reaction of **32a** with the very reactive dienophile, N-phenyltriazolinedione (PTAD) gave a 1:2 adduct, an anti-syn

bisadduct. The first addition was deduced to occur from the anti face due to steric hindrance from the methylene hydrogens. The second addition occurred from the face syn to the bridge. The reaction of **32a** with less reactive dienophiles such as maleic anhydride, benzoquinone and dimethylfumarate gave only 1:1 adducts which were anti-adducts. In another series of reactions, **32b** (the substrate wherein the methylene groups were replaced by carbonyl groups) reacted with the triazolines, PTAD and N-methyltriazolinedione (MTAD) to give predominantly syn addition products. Steric barriers at both faces were considered to be similar in **32b** and the preference for the syn face was accounted for by favourable secondary orbital interactions between the N-lone pair nonbonding orbital on the triazoline with the carbonyl π^* of **32b**.[46g]

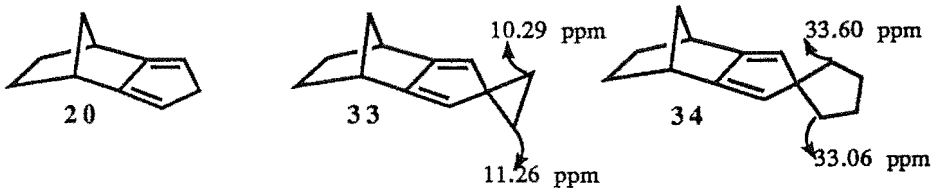
To consolidate their hypothesis, they investigated reactions of substrates such as **32d(i)-(iii)** where increasing steric hindrance is introduced to the syn face, at the same time maintaining the dicarbonyl moieties with their π^* orbitals. Reaction of **32d(i)** with PTAD gave exclusive syn product showing that the favourable secondary orbital interactions were still determining the facial selection and the steric effect of the phenyl group was not important. Reaction of PTAD with **32d(ii)** and **32d(iii)** gave anti-syn product ratios of 60:40 and 50:50 respectively. In these latter cases, the effect of steric hindrance had become another important factor in determining the diastereofacial selectivities.

Furthermore, investigation of the reactions of triazolines with the lactone **32c**,[46f] a substrate which is an "intermediate" between the ether (which gave only anti products) and anhydride (which gave only syn products) supported their hypothesis. In **32c**, the steric effect of only two hydrogens exists. As was expected, the Diels-Alder reactions of **32c** with the triazolines gave *ca.* 1:1 mixtures of syn and anti mono adducts.

1.3.2.4 Norbornane-fused dienes

One of the earliest reported Diels-Alder reactions of isodicyclopentadiene **20** was made by Alder et al. where the reported product was the result of "top face" attack.[37] Kobute and coworkers reported that the reactions of **20** with methyl acrylate and methyl propiolate gave the adducts arising from "bottom face" attack of **20**.[47] Systematic studies

of π-facial selectivity in Diels-Alder reactions of isodicyclopentadiene **20** were later conducted by two major groups of researchers, Paquette[48] and Bartlett[49,50].



Reactions of **20** with alkene dienophiles such as methyl acrylate, benzoquinone and phenyl vinyl sulfone gave exclusively "bottom face" adducts. Similarly, reactions of **20** with methyl propiolate and benzyne gave exclusively "bottom face" adducts. The reverse facial selectivity was observed for sterically demanding dienophiles such as tetracyanoethene (>97% "top face" adduct) and E-1,2-bis(phenylsulfonyl)ethylene (90% from "top face"). The reaction of **20** with maleic anhydride gave varying amounts of "top face":"bottom face" adducts depending on reaction conditions (in fact this reaction was shown to be reversible and was under some degree of thermodynamic control).

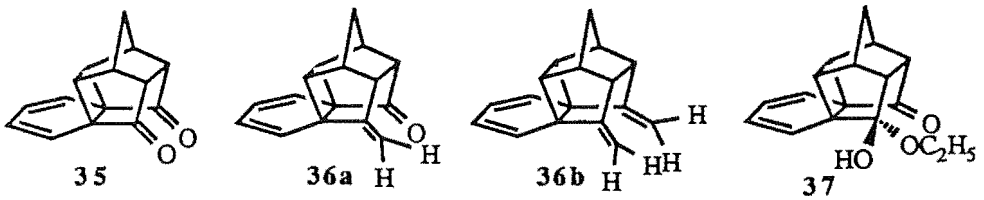
A number of explanations were proposed to account for the stereoselectivity in cycloadditions of isodicyclopentadiene **20** and related species.[51a] Gleiter and Paquette[48a,e] proposed a σ-π tilting hypothesis† whereby the norbornane skeleton causes mixing of σ and π orbitals of the diene, such that the lowest energy orbital (Ψ_1) of the diene tilts its terminal π orbitals inward on top and outward on the bottom. Approach of a dienophile from the bottom to avoid closed shell repulsion between the dienophiles π_s HOMO and the tilted Ψ_1 orbital of the diene would be favoured compared with "top face" attack since repulsive interactions are higher at the "top face". This σ-π tilting hypothesis is supported by some spectroscopic evidence from ^{13}C NMR spectroscopy of the 5-spiro derivatives **33** and **34** where the carbon of the spiro ring projecting to the "top face" was observed to be more shielded than a similar carbon which projects to the "bottom face". Although the effects of substituents on isodicyclopentadiene upon stereoselectivities could be explained by this σ-π tilting hypothesis, variations in stereoselectivity with different dienophiles could not be rationalised.[51]

† The model is based on ab initio and semi-empirical calculations on the ground state and takes no account of the approach of the dienophile which introduces steric and electronic perturbation to the system.

Product stabilities as the determining factor in the stereoselectivity of cycloaddition of isocyclopentadiene **20** and its derivatives was first proposed by Vogel.[52] Subsequently, in the cycloadditions of 7-oxa-2,3-dimethylenenorbornanes, some cases were found to defy explanation by thermodynamic stabilities of the products and polarizability was invoked to account for the preference for the observed "top face" adducts.[53]

Houk et al. considered the torsional and steric effects at the TS leading to the products to be determining factors.[54] They developed a MM2 fixed model to calculate the relative energies of the diastereomeric TS structures of the Diels-Alder reactions of isodicyclopentadiene and derivatives. They reported that trends in the observed stereoselectivities as a function of diene and dienophile substituents were successfully predicted based on their MM2 TS model. Unfortunately, their choice of the alkene dienophile, maleic anhydride† for the study casted some doubts on the correlations.

1.3.2.5 Cage-fused dienes



The cage-fused diene **35** and its derivatives with its rigid cage skeleton are very useful substrates for π-facial selectivity studies as perturbations due to conformational changes are effectively diminished or removed. Isolated cases of Diels-Alder reactions of some dienophiles with diene **35** had been reported[55,56,57] but the stereochemistry of these adducts were not known until a systematic study of π-facial selectivity of **35** with twenty-two dienophiles was reported.[58] As part of that study, crystallographic evidence for the stereochemistry of some of the adducts was also reported.[59] Diels-Alder reactions of **35** with all the dienophiles studied gave only *endo* adducts since *exo* addition would be destablised by nonbonded steric interactions of the cyclobutane ring hydrogens on the "top face" and substituents at the "bottom face". *Endo* addition with some dienophiles

† Reaction of **20** with maleic anhydride is known to be reversible and reported experimental diastereomeric ratios vary according to experimental conditions.

would also be favoured by secondary orbital interactions.[27] Reaction of **35** with alkene dienophiles gave exclusively "bottom face" adducts while acetylenic and azo dienophiles showed mixed π-facial selectivities. A crystallographic study of the hemiacetal **37** was conducted to determine the geometry of the diene moiety, which was found to be essentially planar. This ruled out pyramidalization of the diene system as a determining factor.[60] The planarity of the diene moiety in **35** has since been demonstrated by an X-ray structure of **35**.[61] The observed π-facial selectivities were ascribed to steric effects for reactions with the alkene dienophiles. The mixed selectivities with the acetylenic and azo dienophiles were attributed to a combination of three factors: (i) reduced kinetic differentiation between the two π faces as the latter dienophiles were more reactive, (ii) the dienophiles are less sterically demanding and (iii) the latter dienophiles possess π or nonbonding orbital electron density which will repulsively interact with electron density on the carbonyl oxygen atoms.

As a continuation of that initial study, a recent study of π-facial selectivity in **36a** and **36b** was reported.[62] In these two substrates, the carbonyl oxygens of **35** have been selectively replaced by methylidene groups, thereby retaining the π electrons while introducing increasing steric hindrance at the "bottom face". Reaction of **36a** or **36b** with the alkene dienophiles maleic anhydride (MA) **38** or benzoquinone (BQ) **39** gave exclusively "bottom face" adducts except for the reaction of **36b** with **38** which gave 15% of the "top face" adduct. Reaction of **36a** or **36b** with dimethylacetylene dicarboxylate (DMAD) **40** gave 25% and 10% of the "bottom face" adducts respectively. The trend in the facial selectivities for the reactions of **36a** or **36b** with the azo dienophile, N-phenyl triazolinedione (PTAD) **41** was reversed, and "bottom face" adducts of 78% and 98% respectively were reported. Three previously reported hypotheses for π-facial selectivities were considered: (i) product stabilities[52] (ii) torsional and steric interactions at diastereomeric "transition state" structures [54] and (iii) σ-π orbital mixing leading to π-orbital tilting.[48a,e] Product stabilities as a determining factor were ruled out. Hypotheses (ii) and (iii) both can account for the qualitative results obtained for the reactions of **35** and **36** with the alkene dienophiles but cannot account for the facial selectivity for the reactions with DMAD and PTAD. Unfavourable orbital

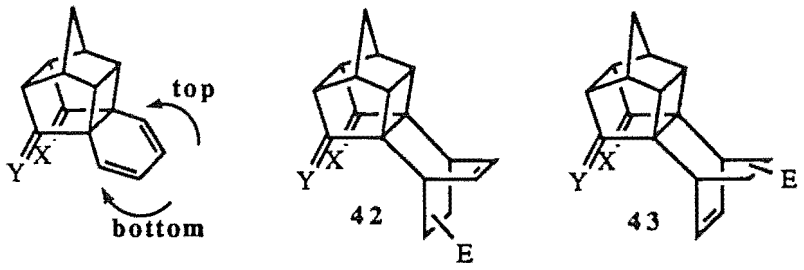
interactions of the closed shells of the carbonyl(s) and methylidene(s) syn to the incoming orthogonal π orbital of DMAD were considered to be important.

As an extension of these studies, other derivatives of **35** were synthesised in the present study and Diels-Alder reactions with selected dienophiles were performed to determine the π-facial selectivities. Attempts were made to rationalise the results obtained. These synthetic studies and cycloadditions are reported in Chapters 2 to 5 of this thesis. A summary of the findings is contained in Chapter 6.

Chapter 2

Syntheses, incidental chemistry and Diels-Alder reactions of monosubstituted cage dienes

The Diels-Alder reactions of hexacyclo[10.2.1^{2,11}.0^{4,9}.0^{4,14}.0^{9,13}]pentadeca-5,7-diene-3,10-dione **35** have previously been studied with a range of dienophiles.[58] Reactions with olefinic dienophiles occur exclusively by attack on the "bottom face" to form **42** while other dienophiles (benzyne, acetylenes and azo compounds) exhibit mixed π-facial selectivities giving rise to mixtures of **42** and **43**. From this initial study, we have been able to group the dienophiles into various classes and are now particularly interested in the effect of variation of the structure of the cage component on reactions with a number of representative dienophiles from each class.



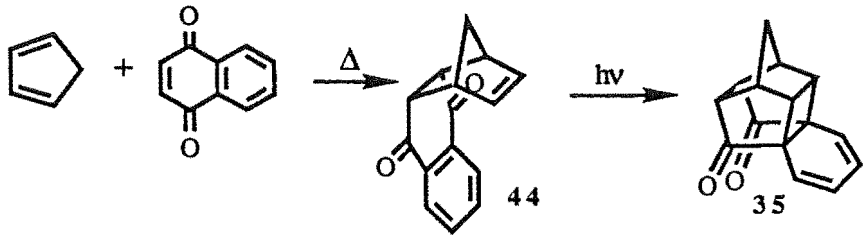
35 X = Y =O
36a X = O, Y = CH_2
36b X = Y = CH_2
52 X = O, Y = -OCH_2CH_2O-
53 X = O, Y = -SCH_2CH_2S-

2.1 Syntheses of monosubstituted cage dienes and incidental chemistry of these cage compounds

2.1.1 Photolyses of Diels-Alder adducts

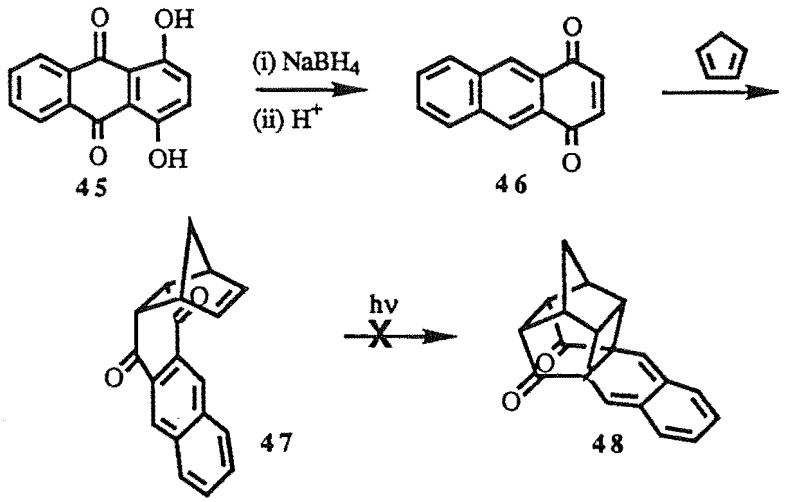
The diketone **35** was prepared according to the literature procedure[57a] which involves, first a [$_\pi$4 + $_\pi$2] Diels-Alder reaction between cyclopentadiene and 1,4-naphthoquinone to produce the *endo*-cyclopentadiene-napthoquinone adduct **44** which on photolysis undergoes a [$_\pi$2 + $_\pi$2] photocycloaddition reaction, wherein the aromaticity of the naphthoquinone moiety is destroyed, to form **35** [**Scheme 2.1**].

Scheme 2.1



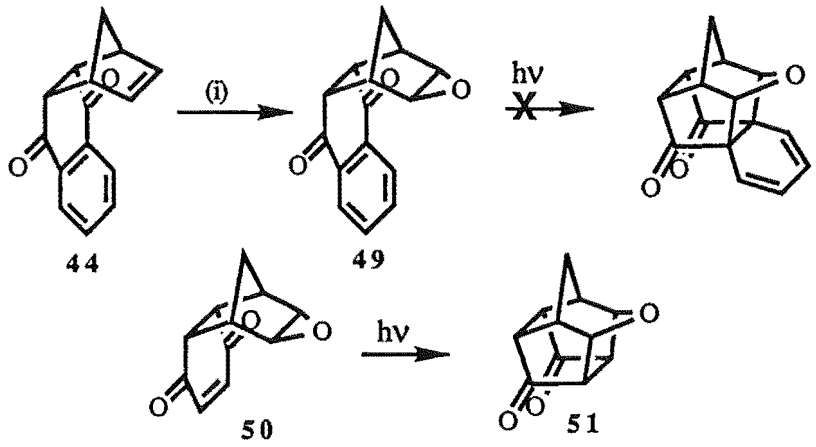
This is in contrast to the attempted [$_{\pi}2 + _{\pi}2$] photolysis of the *endo*-cyclopentadiene-anthraquinone adduct **47**, which was prepared by the literature procedure.[63,64] This involves first a reduction of 1,4-dihydroxyanthraquinone **45** followed by acid catalysed dehydration to form 1,4-anthraquinone **46.** A [$_{\pi}4 + _{\pi}2$] Diels-Alder reaction of **46** with cyclopentadiene gave exclusively the *endo* adduct **47.** However **47** was stable towards photolysis and the expected heptacyclic cage product **48** was not formed [**Scheme 2.2**]. Photocycloaddition of **47** to form **48** is likely to be unfavourable because it involves the loss of aromaticity of two conjugated aromatic rings.

Scheme 2.2



Epoxidation of the cyclopentadiene-naphthoquinone adduct **44** with m-chloroperbenzoic acid gave exclusively the *exo*-epoxy-cyclopentadiene-naphthoquinone adduct **49.** Photolysis of this adduct did not effect a [$_{\sigma}2 + _{\pi}2$] cycloaddition despite a reported [$_{\sigma}2 + _{\pi}2$] photoclosure reaction[65] in the corresponding mono-epoxy-cyclopentadiene-benzoquinone adduct **50** to give an oxa-pentacyclic cage compound **51** [**Scheme 2.3**]. Adduct **49** unlike **50** possesses an aromatic ring and on cycloaddition aromaticity would be destroyed. The energetics of this reaction might not be favoured for this reason.

Scheme 2.3

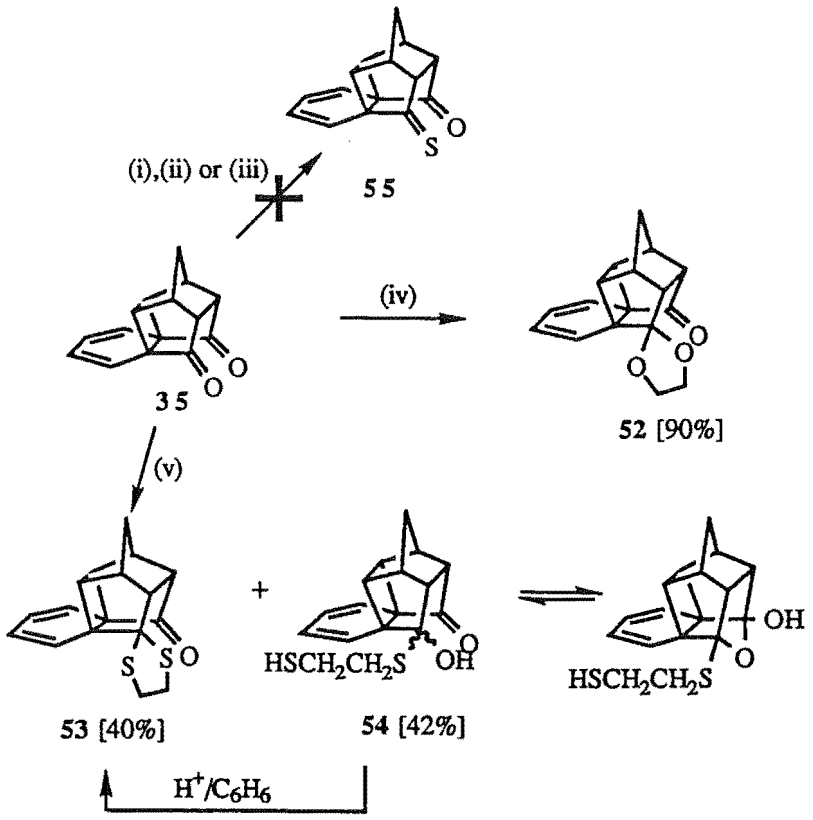


(i) m-chloroperbenzoic acid, CH_2Cl_2, room temperature, 3 days

2.1.2 Syntheses of monoacetal **52** and thioacetal **53**

Attempts to modify one of the ketone functional groups were first investigated. The monoethyleneacetal **52** and the thio-derivative **53** were prepared in the following manner [**Scheme 2.4**].

Scheme 2.4



(i) H_2S/CF_3COOH (ii) Lawesson Reagent/benzene/toluene (iii) P_4S_{10}/diglyme
(iv) $HOCH_2CH_2OH$/p-TsOH/benzene(-H_2O) (v) $HSCH_2CH_2SH/BF_3$/ethyl acetate

The monoethylene acetal **52** was prepared by reaction of diketone **35** with an excess of ethylene glycol in the presence of the acid catalyst, p-toluenesulphonic acid (p-TsOH) in

benzene as solvent. Water was removed by azeotropic distillation of benzene/water using a Dean and Stark trap.[66] When more than two molar equivalents of ethylene glycol were used no bis-acetal was formed due to the large steric interaction between the two acetal groups. The reaction to give the monoacetal proceeded smoothly in high yield (*ca.* 90%). ^{1}H NMR and ^{13}C NMR spectroscopy showed clearly that the product has lost its mirror symmetry as is expected for **52.**

The corresponding reaction of **35** with excess ethane dithiol in ethyl acetate with boron trifluoride etherate as a catalyst[67] gave the mono-ethylenethioacetal **53** (*ca.*40%) which was identified by the similarity of its NMR spectra to those of **52.** A second product **54** (*ca.* 42%) identified as the hemithioacetal precipitated from the reaction mixture. This latter product showed extensive broadening of peaks in its ^{1}H NMR spectrum at room temperature indicative of a dynamic process occurring on the NMR time scale. This broadening may be accounted for by transannular cyclisation involving either the *endo*-hydroxyl or thiol group and the carbonyl moiety. An infrared spectrum of **54** showed the characteristic absorption frequencies of both the hydroxyl and ketone functional groups at 3430 and 1730 cm^{-1} respectively. The identity of this compound as the hemithioacetal **54** was supported by its ready conversion to **53** by heating in benzene/p-TsOH with removal of water by azeotropic distillation of benzene. Despite the use of anhydrous solvents, the lack of a means of removing water formed from the original reaction would account for the formation of **54.**

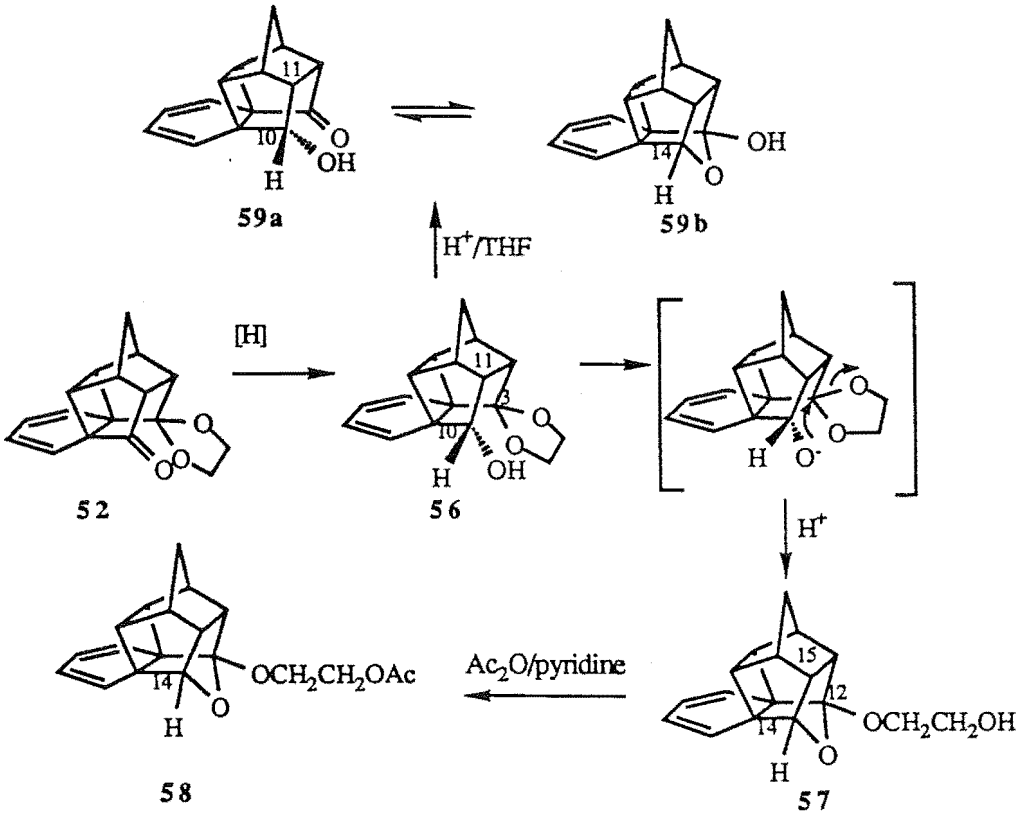
Various attempts at preparing the mixed thione-ketone **55** by reaction of **35** with (i) hydrogen sulfide in trifluoroacetic acid,[68] (ii) Lawesson reagent in benzene/toluene,[69] (iii) tetraphosphorus decasulfide in diglyme,[70] all resulted in either recovery of unconverted starting materials and/or polymeric products [**Scheme 2.4**].

2.1.3 Reduction of **52** and subsequent transannular reactions

Reduction of **52** with either lithium aluminium hydride or sodium borohydride/cerium trichloride gave the *endo*-alcohol **56** as a result of hydride attack at the *exo* face of the carbonyl group. This parallels results obtained by other workers in reductions of similar cage diketones.[71,72] The stereoselectivity of hydride reduction

follows from the appearance of H10 as a doublet of doublets at 3.46 ppm showing that it is coupled to H11 and the hydroxyl group. In its epimer, H10 would be a singlet and resonate downfield by *ca.* 1 ppm.[71] In a solution of chloroform or pyridine over a week at room temperature, **56** undergoes a transannular reaction to form the cyclic acetal **57**, which is only possible if the hydroxyl group has the *endo*-configuration.

Scheme 2.5



This occurence was deduced from both ^{1}H NMR and ^{13}C NMR spectra. In the ^{1}H NMR spectrum of the unbridged *endo*-hydroxylacetal **56** the *exo*-H10 resonates at 3.46 ppm (dd, $J_{H10,OH}$ = 12.3Hz, $J_{H10,H11}$ = 2.9Hz) and the hydroxyl absorption appears at 5.34 ppm (d, $J_{OH,H10}$ = 12.1 Hz). Coupling between hydroxyl protons and geminal protons is normally only observed if the exchangeable hydroxyl proton is slowed by some phenomenon such as intramolecular H-bonding between it and a proximate oxygen lone pair. Such a situation exists between the *endo* hydroxyl proton and the acetal moiety. The ^{13}C NMR of **56** showed the expected resonance of C10 at 76.1 ppm which is typical of CHOH. On transannular cyclisation to **57**, downfield shifts at the atom 12 and 14 centers were observed (δ H14 = 4.41 ppm, d, $J_{H14,H15}$ = 4.4 Hz) and the hydroxyl proton resonates as a broad singlet at *ca.* 2.75 ppm ($W_{h/2}$ = 20 Hz). The

corresponding C14 and C12 signals were at 86.8 ppm and 122.7 ppm respectively. Further evidence which confirmed the bridged nature of **57** follows from its acetylation with acetic anhydride-pyridine to give **58**. The acetylation of the hydroxyl group of the ethylene moiety was apparent from the chemical shift of H14 which remained unchanged at 4.41 ppm (d, $J_{H14,H15}$ = 4.7 Hz). Instead, the chemical shift of the methylene protons which are adjacent to the acetate group is shifted from 3.75 ppm to 4.25 ppm, a downfield shift of 0.5 ppm. If acetate formation was on the CHOH group in **56** (see later), it would shift the H10 proton downfield by *ca.* 0.6 ppm [**Scheme 2.5**].

In general, transannular reactions in such rigid cage systems, and internal hemiacetal formation in particular, are quite common.[74,75,76] Hydrolysis of *endo*-hydroxylacetal **56** produced an equilibrium mixture of **59a** and **59b**, which is observed by the broadening of peaks in the ^{1}H NMR spectrum of the crude reaction mixture. After elution through silica gel, which slowed down the rapid exchange process on the NMR time scale, the peaks sharpened and the proton H10 resonates at 3.82 ppm (d, J = 3.3 Hz)[§] and H14 at 4.41 ppm (d, J = 4.4 Hz) for the unbridged ketol **59a** and bridged hemiacetal **59b** respectively. Furthermore the ^{13}C NMR spectrum of this mixture showed twenty-four protonated carbon signals which can only be accounted for by an equilibrium mixture of two unsymmetrical structures such as **59a** and **59b** [Scheme 2.5]. In the pentacycloundecane (PCUD) cage system where the distance between the 8 and 11 functional groups in **60** is comparable to that in **35**[†] *endo*-hydroxyketone **61** exists as a similar equilibrium mixture.[76] The distance between the reacting functional groups in such rigid cage systems is crucial in promotion of such transannular activity as illustrated by a reported finding by Dekker et al.[77] where hydrolysis of the homologous pentacyclododecane hydroxy-acetal **62** gave the hemiacetal **63**. This is considered to result from the shorter distance between the participating

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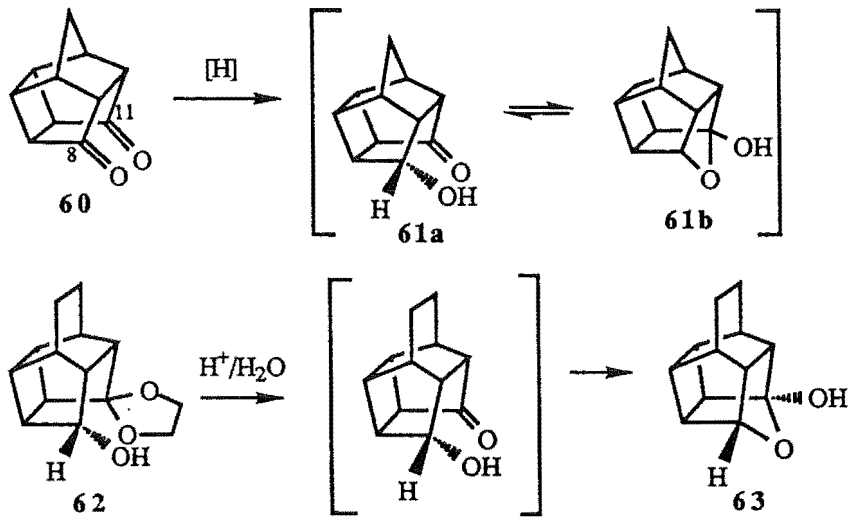
§ Predicted $J_{H10,H11}$[73] for MM2 minimised structures of **59a** and its epimer (at C10) are 4.3 Hz (dihedral angle = 53°) and 2.3 Hz (dihedral angle = 67°) respectively.

† The experimentally measured distances between the carbonyl groups in cage diketone **35** are 2.563Å and 3.856Å for the C-C and O-O distances respectively. These data were obtained from refs 61 and 62. This compares favourably with estimated values from Dreiding stereomodels of PCUD dione **60** for the corresponding distances at 2.44Å and 3.50Å respectively.[74] The estimated value (2.44Å) was considered by Marchand[75] to compare favourably to experimentally measured distances in similar PCUD compounds.

functional groups [**Scheme 2.6**].

Scheme 2.6



2.1.4 Reactions of cage diketone **35** with alcohols

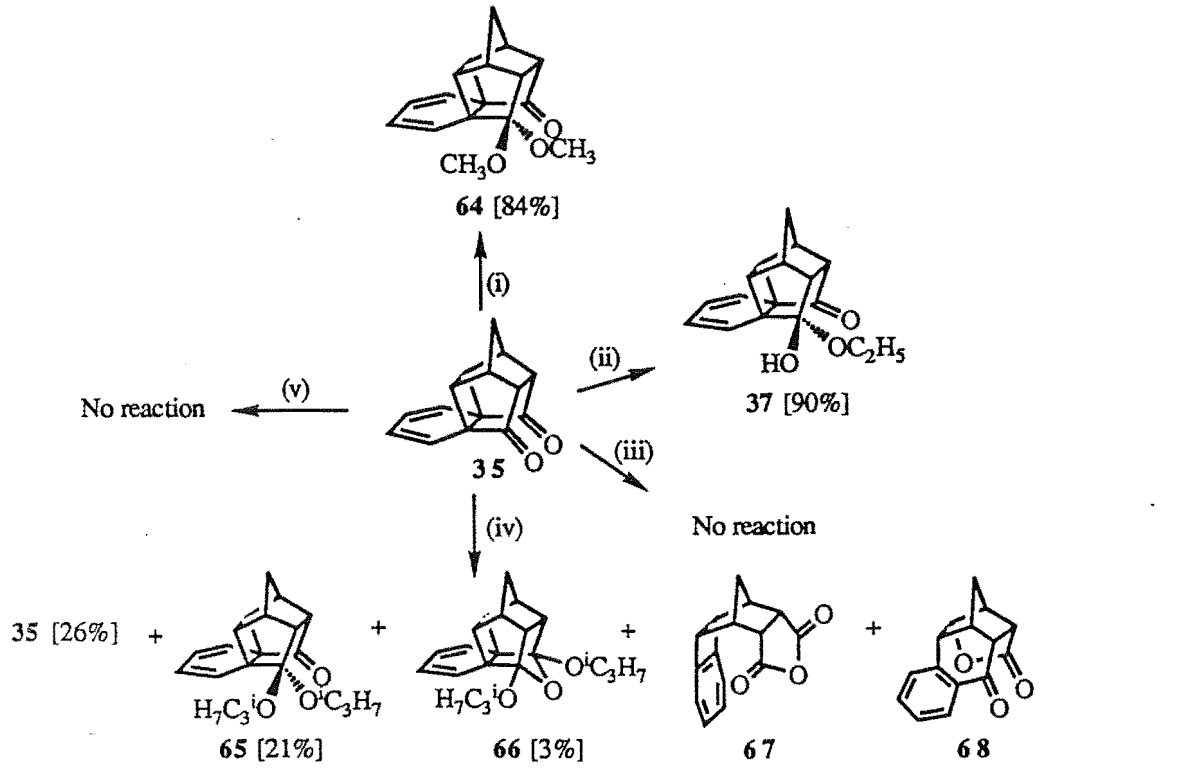
It had previously been reported that recrystallisation of **35** from ethanol resulted in its conversion to the crystalline monohemiacetal **37** and an X-ray structure proved that ethanol addition occurred to the *endo* face of the carbonyl group.[58] This result appears to be in contrast to other reactions involving the carbonyl group of related cage compounds which involve nucleophilic attack on the *exo* face of the carbonyl group.[74,78,79] In an effort to investigate further this unexpected finding, diketone **35** was reacted with various alcohols in the presence of an acid catalyst, p-toluenesulphonic acid. The reaction conditions and the products that were obtained are shown in Scheme 2.7.

Reaction with methanol gave exclusively the acetal **64** which was identified from the presence of the two non-equivalent methoxy signals in its ^{1}H NMR spectrum at 3.11 ppm (*endo*-OCH_3) and 3.28 ppm (*exo*-OCH_3). A ^{13}C NMR spectrum of **64** showed the corresponding methoxy signals at 48.1 ppm and 49.8 ppm as well as a carbonyl carbon resonance signal at 210.9 ppm. The presence of the carbonyl group was also evident from infrared spectroscopy which showed a characteristic strong absorption at 1730 cm^{-1}.

An attempt was made to prepare the diethoxyacetal by reacting diketone **35** with ethanol under more forcing conditions, namely in benzene at 80°C with p-toluenesulphonic acid as a catalyst and removal of water by azeotropic distillation of

benzene using a Dean and Stark trap. Neither hemiacetal **37** nor acetal was detected by NMR analysis of the reaction mixture; the diketone **35** was recovered. This is perhaps not surprising as the hemiacetal **37** is known to revert to the diketone **35** in addition reactions to dienophiles at *ca.* 70°C.[58]

Scheme 2.7

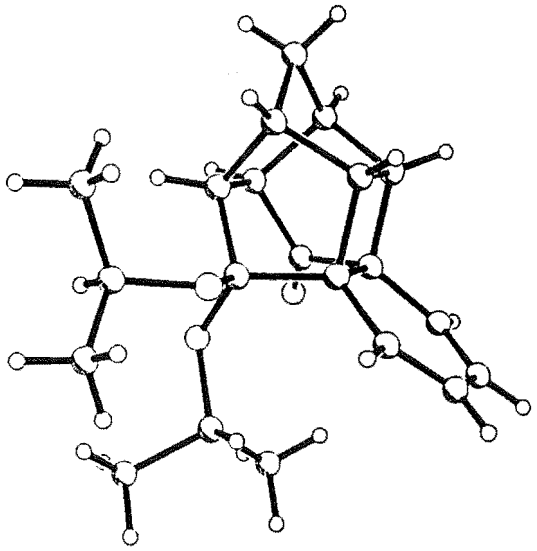


(i) dry methanol, p-TsOH, reflux 5 h
(ii) ethanol, room temperature
(iii) ethanol, p-TsOH, reflux in benzene, 5 h (-H_2O)
(iv) isopropanol, p-TsOH, reflux 6 days
(v) t-butanol, p-TsOH, reflux in CH_2Cl_2, 3 days

In order to probe further into the steric demand of the nucleophile, the bulk of the alkyl group was increased to isopropyl and tertiary butyl groups. Addition of isopropanol to diketone **35** required more stringent conditions and, after six days of reflux in isopropanol catalysed by p-toluenesulphonic acid, the major product was the unsymmetrical monoacetal **65** (*ca.* 21%). A small amount of the symmetrical bis-acetal **66** (*ca.* 3%) was obtained and unreacted cage diketone **35** (*ca.* 26%) was recovered. Trace amounts of rearrangement products **67** and **68**, which arise from oxidation by peroxides present in isopropanol with concommitant rearrangement were also detected. Similar rearrangements have been reported by Mehta and Singh[80] in the ceric ammonium nitrate oxidation of cage diketone **35**. Oxidation occurs even when peroxides are removed. The long reaction time and heat allow for the reformation of peroxides.

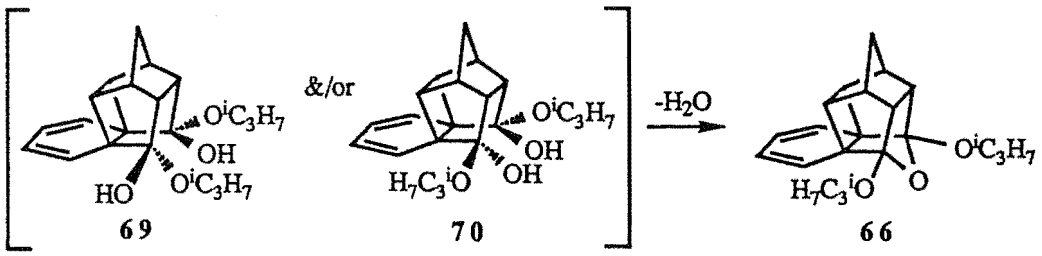
The two acetal products were identified from NMR and infrared spectroscopy. NMR spectra of monoacetal **65** showed a loss of mirror symmetry as expected for an unsymmetrically substituted cage compound. The two isopropyl groups were non-equivalent. The carbonyl moiety was shown to be intact from the ^{13}C NMR and IR spectra. An X-ray determined structure of **65** was obtained and Figure 2.1 shows a perspective view of this structure. The symmetrical nature of bis-acetal **66** was evident from the presence of eleven resonance signals in the ^{13}C NMR spectrum. The absence of a carbonyl group was shown by both ^{13}C NMR and infrared spectroscopy.

Figure 2.1. X-Ray Structure of **65**



The formation of bis-acetal **66** is interesting. The thermodynamically less stable *exo*-hemiacetal is trapped by transannular cyclisation. We propose that **66** is formed by dehydration of **69** and/or **70** [**Scheme 2.8**].

Scheme 2.8

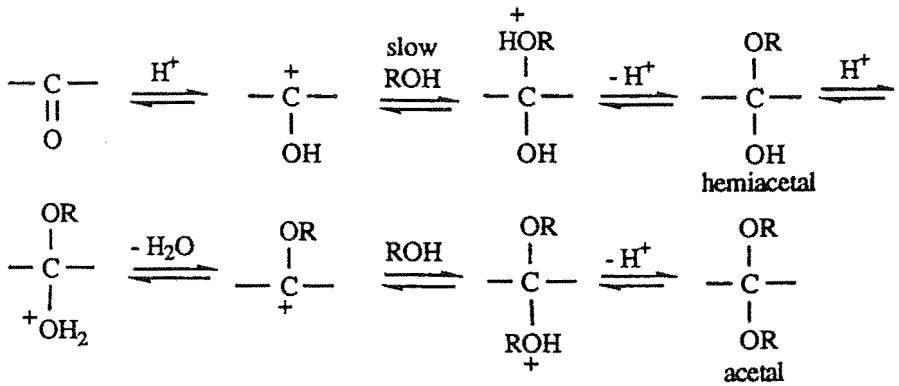


Similar acid-catalysed dehydration reactions giving rise to an oxa-bridge have been reported for PCUD cage compounds with *endo-endo* dihydroxyl or *endo-exo* dihydroxyl

groups at the C8 and C11 centers.[81]

When the size of the nucleophile was increased further by the use of t-butanol, no addition product was detected after three days of reflux in dichloromethane. The steric demand of the nucleophile would imposes severe non-bonded interactions in such a rigid cage system. Dreiding models of the hemiacetal and acetal seemed to support this view.

Acetals are formed by reaction of aldehydes and ketones with alcohols in the presence of an acid catalyst.[82] This is a reversible reaction and acetals can be hydrolysed by treatment with acids but are stable to bases. This makes this reaction a useful method for protection of the carbonyl group from attack by nucleophiles.[83] The mechanism, which involves initial formation of a hemiacetal[84] is the reverse of that for acetal hydrolysis.[85] The equilibrium of the acid catalysed reaction is controlled by the nucleophilic addition of the alcohol to the carbonyl group and not by the conversion of the hemiacetal to the acetal.[86,87] The main problem in the acetal formation in acidic medium is to shift the equilibrium by reducing the water concentration. This is accomplished by (i) addition of a large excess of alcohol and (ii) removal of the water formed by azeotropic distillation, ordinary distillation or the use of a drying agent such as molecular sieves or alumina.[82]

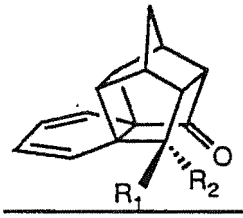


It has been previously reported that the alcohol structure has a marked influence on the equilibria of acetals with the extent of conversion markedly decreasing in the order primary > secondary > tertiary.[88] This was observed in our case where reaction of cage diketone **35** with methanol led to the isolation of only the thermodynamically more stable acetal product **64**. Reaction of diketone **35** with isopropanol led to an equilibrium mixture of the diketone **35**, acetal **65** and bridged bis-acetal **66**.

The formation of the *endo*-ethoxyhemiacetal **37** by the recrystallisation of cage

diketone **35** in ethanol is interesting, as hemiacetal intermediates are not often isolable since acetals are more stable in a reaction under thermodynamic control. Molecular modelling† of the *endo*- and *exo*-alkoxyhemiacetals formed by the reaction of **35** with methanol, ethanol and isopropanol was done to give an estimate of the relative product stabilities of these intermediate addition products. Table 2.1 below outlines the results obtained. The table indicates that the *endo*-hemiacetals are the thermodynamically more stable intermediates. The exclusive formation of the *endo*-ethoxyhemiacetal **37** is probably governed by the relative insolubility of **37** in ethanol.

Table 2.1. "Total energy" of the *endo*- and *exo*-hemiacetals of the reaction of cage diketone **35** with methanol, ethanol and isopropanol calculated using BAKMDL (1991).

Hemiacetal	No. of conformers found within 12.6 kJ mol^{-1}	Boltzmann average energy (kJ mol^{-1})
		
$R_1 = OH, R_2 = OCH_3$	4	342.1
$R_1 = OCH_3, R_2 = OH$	2	345.4
$R_1 = OH, R_2 = OC_2H_5$	4	342.9
$R_1 = OC_2H_5, R_2 = OH$	2	346.8
$R_1 = OH, R_2 = O^iC_3H_7$	10	353.8
$R_1 = O^iC_3H_7, R_2 = OH$	6	357.6

2.2 Diels-Alder reactions

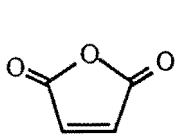
Diels-Alder reactions of **35** with a large number of dienophiles, twenty-two in total, were extensively studied and the observed π-facial selectivities have been ascribed to a combination of steric and electronic factors.[58] The dienophiles used in that initial study may be classified into four groups, (i) fourteen alkene type, (ii) two alkyne type, (iii) three azo type and (iv) one benzyne type. The results from that study show that all the olefinic dienophiles add exclusively from the carbonyl-bearing face of the diene **35** while

† The calculations were performed using BAKMDL (1991) which uses MMP2 force-fields in order to allow conformational searching of the alkoxyl and hydroxyl groups.

other dienophiles (benzyne, acetylenes and azo compounds) show mixed π-facial selectivities.[58]

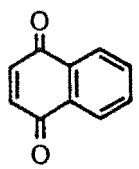
More recently, a related study described the reactions of representative dienophiles with monomethylidene **36a** and dimethylidene **36b** derivatives of **35**, in which the carbonyl oxygen is progressively replaced by a methylidene group which maintains the π electron density at these center(s) but removes the oxygen lone pairs.[62] In the present study, cage dienes **52** and **53** represent the cases where one carbonyl oxygen of diene **35** has been selectively replaced by groups (O or S) containing lone pair electrons, effectively removing the π electrons at either the C3 or C10 center but still keeping lone pair electrons in a region proximate to one face of the diene. By reacting **52** or **53** with the representative dienophiles shown in Chart 2.1, we expect to be able to investigate the effects of lone pairs on π-facial selectivity.

Chart 2.1

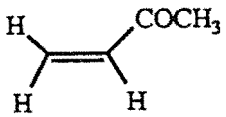


38

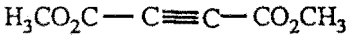
39



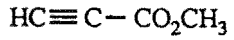
71



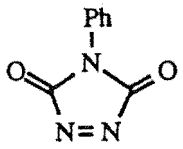
72



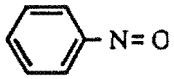
40



73



41

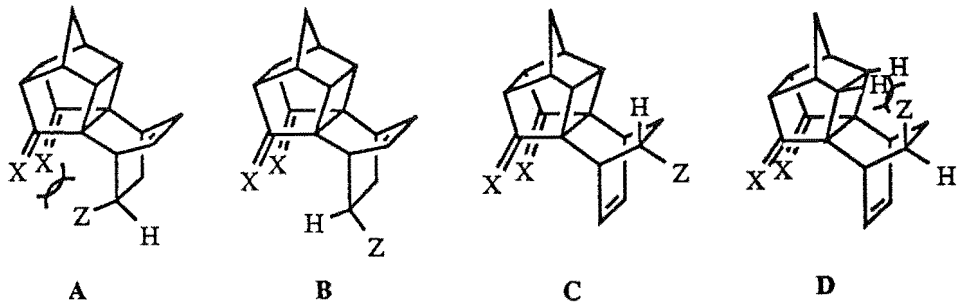


74

Reaction of symmetrical cage dienes[§] with an olefinic dienophile may, in principle, give rise to four products, two Alder adducts **B** and **C** and two anti-Alder adducts **A** and **D** [Chart 2.2]. In this study, as was found previously, only the Alder adducts **B** and/or **C** were formed since the products arising from anti-Alder addition of the diene component would necessitate undue non-bonded steric interactions between the substituent on the dienophile and the functional group on the diene in **A** or the hydrogens on the cyclobutane ring in **D**. In many cases where the dienophiles have orbitals of suitable symmetry and energies, additions leading to Alder adducts are further stabilised through favourable orbital interactions.[27]

[§] Unsymmetrical dienes can give both regio- and stereo-isomers.

Chart 2.2



A **B** **C** **D**

The Diels-Alder reactions were performed in non-polar solvents (benzene or toluene) except for the case of N-phenyltriazolinedione **41** which was reacted at 0-5°C in dichloromethane. In many cases, the reactions were much slower than the corresponding reactions of **35** but no attempts were made at increasing the rates of reaction by catalysis with Lewis acids[44,89a-c] as this would introduce a further parameter into this study. Furthermore, Lewis acid catalysis of some Diels-Alder reactions can affect the stereochemical course of the reactions particularly where the dienophile is activated by a carbonyl or nitrile group.[44,89a] The progress of these reactions was monitored by either thin-layer chromatography (t.l.c.) or ^{1}H NMR. Furthermore, where the reactions were slow, monitoring of reaction mixtures by ^{1}H NMR over the reaction period did not indicate any equilibration of the adducts formed; i.e. the ratio of the products remain constant throughout the reaction period. Therefore these Diels-Alder reactions are essentially irreversible with the exception of a few of the reactions involving nitrosobenzene **74**, in which reversibility was sometimes observed (see later).

The stereochemistry of the adducts could be assigned by nuclear Overhauser effect difference spectroscopy (NOED).[90] In fact, because of the rigidity imposed by the cage structure, strong mutual NOE enhancements are typical of proximate protons in such compounds. This was used to distinguish the products resulting from attack from the "bottom face" of the cage substrates which showed mutual NOE enhancements between the olefinic and cyclobutane ring protons.[58] In cases where the proton resonances are resolved, full assignment of proton signals of these adducts were made based on chemical shift values and NOED spectra. Heteronuclear proton-carbon correlation spectroscopy (HETCOR) using a sequence which ensures full ^{1}H-^{1}H decoupling[91] was used to unambiguously assign the ^{13}C NMR spectra. Examples of the use of NOED and

HETCOR NMR techniques are given in the Experimental section.

The monoacetal **52** and thioacetal **53** reacted much more slowly than diketone **35**[58] and the Diels-Alder reactions of these dienes were allowed either to proceed for a longer period or stopped prematurely when sufficient product(s) were indicated by ^{1}H NMR analysis of the reaction mixture. A summary of the product ratios is given in Table 2.2.

Table 2.2. Product Ratios[a] for the Diels-Alder reactions[b] of **52**, **53**, **35**[58], **36a** and **36b**.[62]

Dienophile	% reaction at the "bottom face" of the diene				
	52	**53**	**35**	**36a**	**36b**
MA (**38**)	100	100	100	100	85
BQ (**39**)	95	-	100	100	100
NQ (**71**)	92	-	100	-	-
MVK (**72**)	100[c]	100[c]	100	-	-
DMAD (**40**)	20	2	55	25	10
MP (**73**)	44	-	100	66	-
PTAD (**41**)	37	12	64	78	93
NB (**74**)	10	0	-	-	-

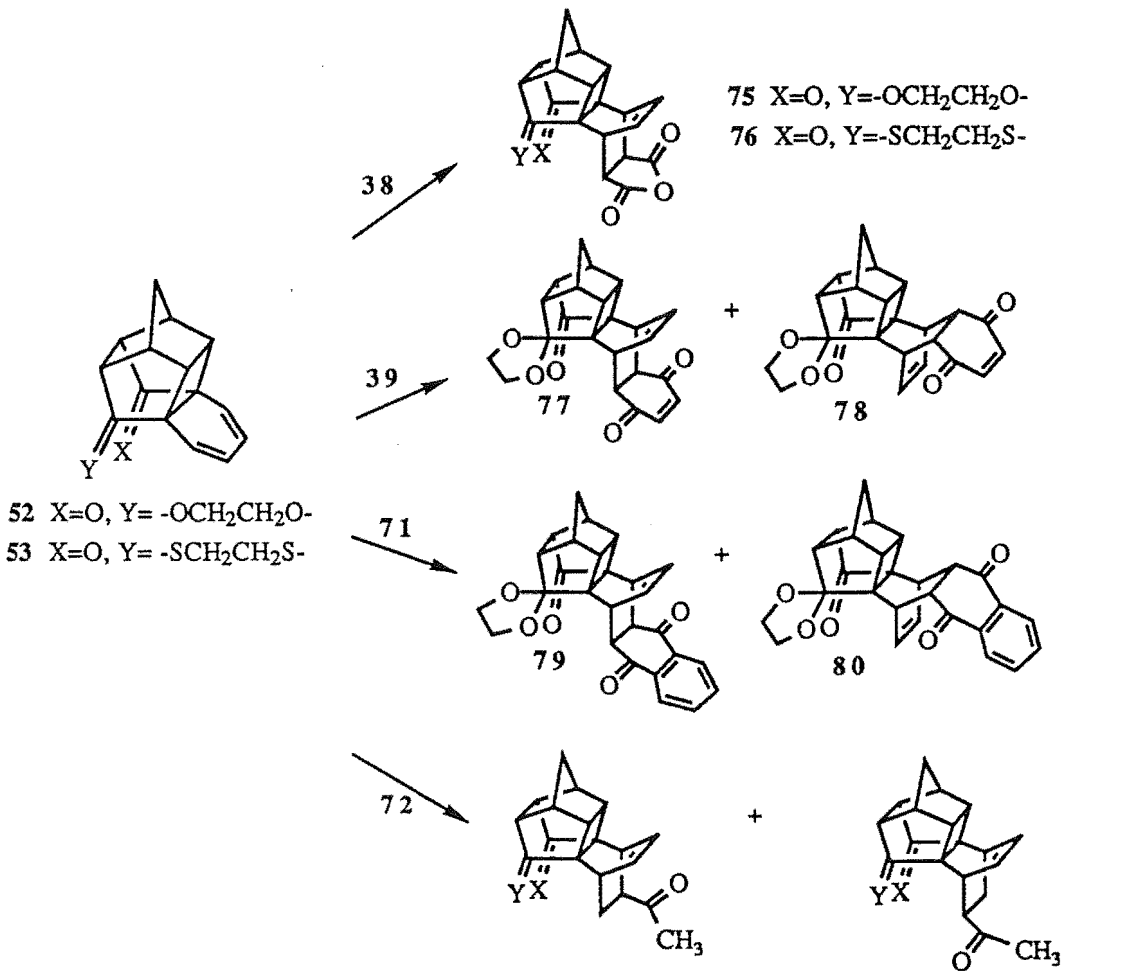
[a]Product ratios (± 2%) from 300 MHz ^{1}H NMR analysis of crude reaction mixtures.
[b]All reactions were conducted in benzene at 80°C except for **52** with NB **74** at 5°C, **53** with DMAD **40** in toluene at 110°C and those involving PTAD **41** at 0 - 5°C in CH_2Cl_2.
[c]Two regioisomers in a ratio of 3:2 were formed.

2.2.1 Reactions with alkene dienophiles

Dienes **52** and **53** reacted with maleic anhydride (MA, **38**) to give exclusively single adducts **75** and **76**, respectively, arising from attack from the "bottom face" of these dienes [**Scheme 2.9**]. This is identical to the selectivity found in reactions of **35** and **36a**. Reactions of **52** with benzoquinone (BQ, **39**) and naphthoquinone (NQ, **71**) are not as facially selective and the "bottom face" adducts **77** and **79** were observed in 95% and 92% stereochemical yield respectively. The introduction of a more bulky acetal group provides some steric hindrance to attack from the "bottom face", thereby forcing competitive reaction from the "top face" leading to the formation of 5% and 8% of **78** and **80** respectively. This parallels the result obtained for the reaction of **36b** with MA,

where the greater steric barrier provided by the dimethylidene hydrogens forces some of the alkene dienophile to attack from the "top face", leading to formation of 15% of the "top face" adduct.[62]

Scheme 2.9



With methyl vinyl ketone (MVK, **72**), **52** and **53** reacted extremely slowly compared to **35** which was reported to have proceeded to completion in 4 days at 80°C.[58] In contrast, the reaction mixture of **52** or **53** with MVK **72** showed the presence of *ca.* 24% unreacted **52** and *ca.* 52% unreacted **53** after 49 days at 80°C and 51 days at 110°C respectively. These reactions were stopped after these periods. Reaction of **52** with MVK **72** produced two adducts **81** and **82**, in the ratio of 3:2 which were purified by radial chromatography. The assignments of stereo- and regio-chemistries for **81** and **82** were confirmed by NOED spectroscopy, which shows the reaction is highly π-facial selective but of mixed regioselectivity. Thioacetal **53** reacted with MVK **34** to give two

"bottom face" adducts in a 3:2 ratio. However these adducts were not as amenable to chromatographic separation and only one of them **83** or **84** was isolated and characterised. Unfortunately, because of the extensive overlap of key proton resonance signals in its ^{1}H NMR spectrum, the use of NOED spectroscopic analysis could not unambiguously confirm the regiochemistry of this adduct.

The facial selectivity of MVK **72** for **52** and **53** is 100% from the "bottom face", as is the case for **35**. However since both the diene and dienophile are unsymmetrical, two "bottom face" adducts could be formed and the reasons for the observed ratio of these adducts in the reaction of **52** are not clear. The fact that removal of one of the carbonyl groups by acetalisation causes such a drastic reduction in reactivity might imply that the carbonyl group is somehow activating the diene. On the whole the alkene dienophiles show a strong preference for the "bottom face" of **52** and **53** and these reactions seem to be under steric control. These dienophiles possess hydrogens attached to the C=C, which may experience repulsive steric interactions with the cyclobutane ring protons in the transition structures leading to "top face" attack.

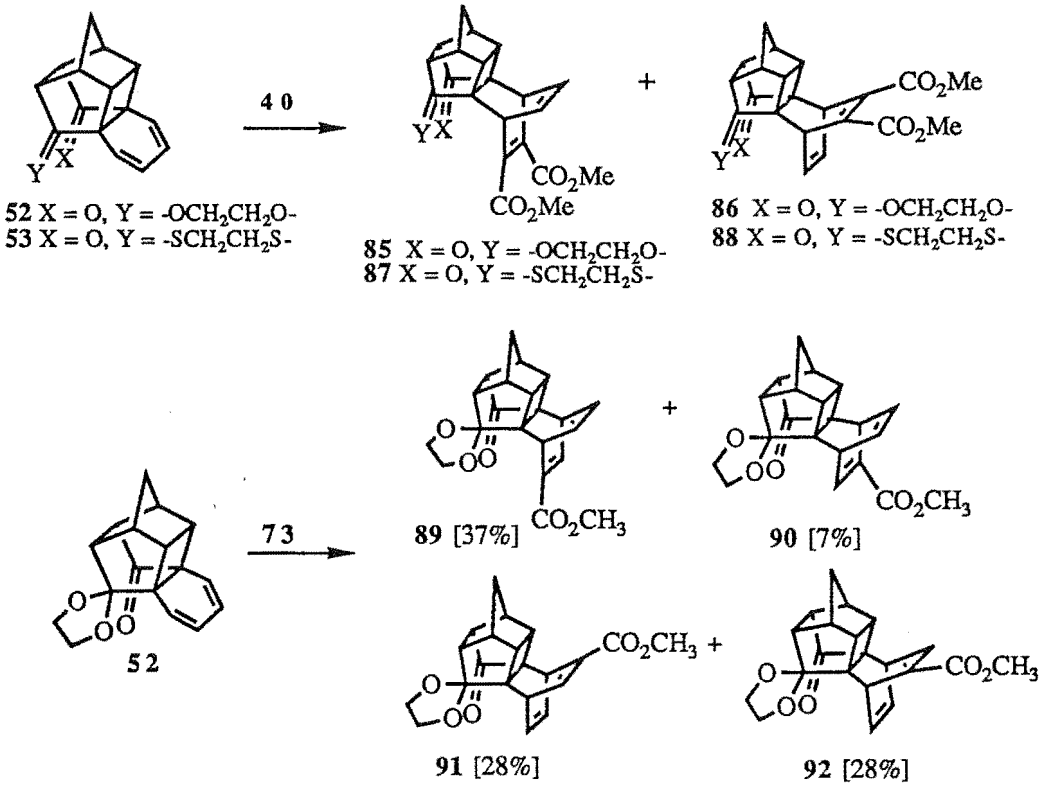
2.2.2 Reactions with alkyne dienophiles

Reaction of **52** or **53** with the electron-deficient alkyne dienophile dimethylacetylene dicarboxylate (DMAD, **40**) produced the adducts **85** and **86** or **87** and **88** respectively [**Scheme 2.10**]. In contrast to the reaction of **35** with DMAD **40** in which the corresponding "bottom face" adduct was formed to an extent of 55%, substitution of one of the carbonyl groups in **35** with an acetal or thioacetal group, as in **52** or **53**, had a significant influence on this selectivity. Reaction of **52** with DMAD **40** produced only 20% of the "bottom face" adduct **85** and 80% of the "top face" adduct **86**. Furthermore, reaction of **53** with DMAD **40** gave only 2% of **87** and 98% of **88**.§

Reaction of **52** with methyl propiolate (MP, **73**) gave a mixture of the four adducts **89** - **92**. MP **73** was not as facially selective for **52** as in the case of **35** and the "bottom face" adducts **89** and **90** were observed as 44% of the mixture, while the "top face" adducts **91** and **92** accounted for 56%. The ^{1}H NMR of the crude reaction mixture

§ The stereochemistries of the adducts were again determined by NOED spectroscopy with the "bottom face" adducts, **85** and **87**, showing mutual enhancements between the olefinic and cyclobutane protons.

Scheme 2.10



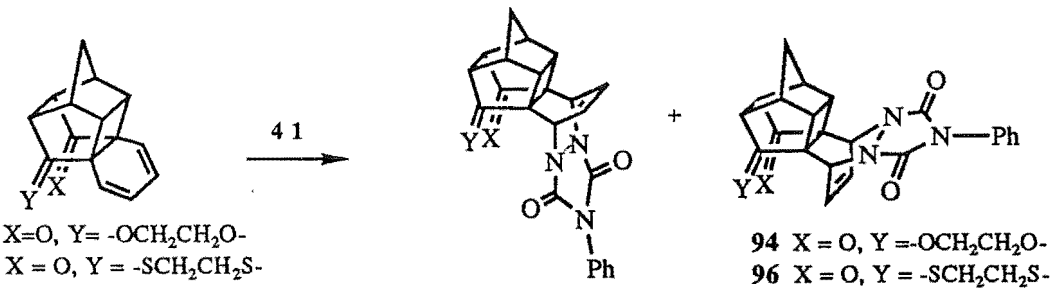
showed only three non-equivalent methoxy signals at δ 3.67 ppm, 3.76 ppm and 3.78 ppm (two coincidental signals) and associated sets of olefinic signals. Three of the adducts were obtained pure by preparative hplc and the stereochemistries were assigned by NOED spectroscopy. On attacking from the "top face", the dienophile shows little discrimination between the two possible "top face" transition structures and hence **91** and **92** are formed in a 1:1 ratio. Approach from the "bottom face" of the diene **52** resulted in a distinct preference for the formation of the "bottom face" adduct **89** which has the methoxycarbonyl group anti to the carbonyl group; the ratio of the observed adducts **89** to **90** is *ca.* 5:1. This regioselectivity is rather unexpected as one would expect **89** to be disfavoured relative to **90**, based on both steric and electrostatic interactions of the dienophile with the terminal carbon of the diene moiety in the transition state leading to the formation of **89**.[92] However, electrostatic effects cannot be the determining factor in this regioselectivity as one would expect the same effect on attack from the "top face" of the diene.

Acetylenic dienophiles possess filled π orbitals which are orthogonal to the σ-bonds being formed in the reaction. These orbitals could interact unfavourably with the lone

pairs on the acetal and carbonyl moieties if the dienophile reacts at the "bottom face", thereby leading to increasing levels of formation of the "top face" adducts. Increasing the size of the heteroatom by replacing oxygen with sulphur enhances "top face" attack.

2.2.3 Reactions with N-phenyltriazoline dione **41**

Scheme 2.11



52 X=O, Y= -OCH_2CH_2O-
53 X = O, Y = -SCH_2CH_2S-

93 X = O, Y = -OCH_2CH_2O-
95 X = O, Y = -SCH_2CH_2S-

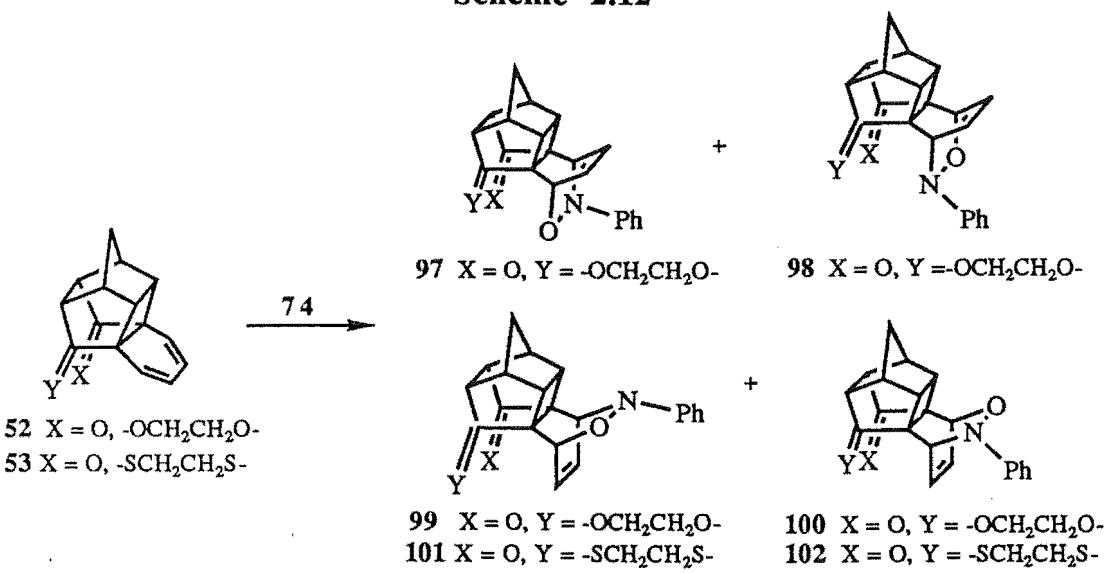
94 X = O, Y =-OCH_2CH_2O-
96 X = O, Y = -SCH_2CH_2S-

Reaction of **52** or **53** with N-phenyltriazoline dione (PTAD, **41**) gave a mixture of the two diastereomeric adducts **93** and **94** or **95** and **96** respectively [**Scheme 2.11**]. PTAD **41** shows a higher preference for attack from the "top face" of dienes **52** and **53** compared to **35**. The acetal **52** reacted with PTAD **41** to give 37% of the "bottom face" adduct **93** compared to 64% for **35** and this trend continues with substitution by a thioacetal group in which only 12% of the "bottom face" adduct **95** was observed. This trend in the π-facial selectivity for this series is opposite to that observed in the methylidene substituted dienes **36a** and **36b** where successive substitution with methylidene group(s) increases the preference for attack of PTAD from the "bottom face" of the diene, giving rise to the formation of 78% and 93% of the respective "bottom face" adducts. Azo dienophiles, such as PTAD **41**, possess lone pair electrons which may interact with lone pairs on the acetals in reactions from the "bottom face" thereby destabilising the transition state structure for reaction at this face. In contrast, since such interactions do not exist for reactions at the "top face" of these dienes, PTAD **41** preferentially reacts from the "top face".

2.2.4 Reactions with nitrosobenzene **74**

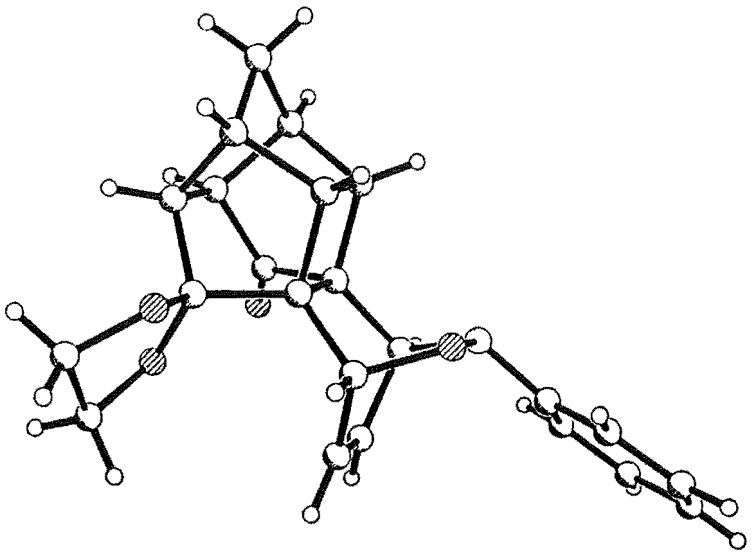
Reaction of diene **52** with nitrosobenzene (NB, **74**) produces all of the four possible adducts **97** - **100** [**Scheme 2.12**]. An attempt at purification of the crude

Scheme 2.12



reaction mixture by preparative chromatography gave only fractions of a mixture of two adducts which proved to be the "top face" adducts **99** and **100** as determined by NOED spectroscopy. (Irradiation of the olefinic signals did not result in an enhancement of the cyclobutane ring protons). These two adducts **99** and **100** were formed in a ratio of 2.5:1 respectively. On recrystallisation of this mixture, a pure sample of **99** was obtained and was fully characterised. An X-ray crystal structure determination of **99** further confirmed its stereochemistry and regiochemistry. Figure 2.2 shows a perspective view of the structure of **99**. Relating this information to the spectrum of the crude reaction mixture, we determined that the π-facial selectivity of **74** for **52** is 10% for the "bottom face" resulting in the formation of adducts **97** and **98** in a ratio of 2:1, although the regioselectivity is uncertain.

Figure 2.2. X-Ray Structure of **99**.



Reaction of NB **74** with **53** showed exclusive selectivity for the "top face" of the thioacetal **53** resulting in the formation of two adducts **101** and **102** in a 2.2:1 ratio but the regioselectivity is not certain. Attempts at chromatographic separation of these adducts on silica were unsuccessful.

2.3 Molecular mechanics calculations

Early kinetic and thermodynamic investigations of π-facial selectivity led to the proposal that product stability[52] was important in influencing π-facial selectivity, although this has been shown to be of limited generality.[53] In order to investigate any relationship of product stability to the reactions of **52** and **53** the MMX[§] steric energy was calculated for each of the possible products resulting from reaction of **52** and **53** with the dienophiles employed.[†]

Table 2.3. Calculated (MMX) energy differences ($\Delta E_{(bottom\ -\ top)}$, kJ mol^{-1}) between adducts resulting from "bottom face" and "top face" reaction ($\Delta E_{(B-T)}$) and calculated percentage "bottom face" reaction at 80°C (% calcd) of **52** and **53** with selected dienophiles compared with experimental result (exp).

Dienophiles		52			53	
	$\Delta E_{(B-T)}$ kJ mol^{-1}	% calcd kJ mol^{-1}	% exp	$\Delta E_{(B-T)}$	% calcd	% exp
MA (**38**)	- 3.2	75	100	- 2.9	73	98
BQ (**39**)	- 4.0	78	95	-	-	-
NQ (**71**)	- 12.1	98	92	-	-	-
DMAD (**40**)[a]	- 7.9	94	20	- 6.4	90	2
PTAD (**41**)[b]	0.06	50	37	- 0.4	54	12

[a]Calculated using BAKMDL (MM2) energy difference between the average energy of significant conformers at 80°C.
[b]Calculated at 0°C.

Based on product stability, these calculations for reactions of **52** or **53** with alkene dienophiles [**Table 2.3**] predicted the major product to be the one resulting from reaction from the "bottom face". For MA **38** and BQ **39**, a range of 73 - 78% of the

[§] The calculations were performed using MMX88 or MMX90 and associated parameters as available from Serena Software, 489 Serena Lane, Bloomington, IN 47401.

[†] For DMAD the MM2 force-field as implemented in the BAKMDL (1989) program was used in order to allow conformational searching of the methoxycarbonyl groups.

"bottom face" adducts was calculated, while for reaction of NQ **71** with **52** a predicted value of 98% was obtained. The disparity between the predicted percentages of the "bottom face" adducts with experimental results was even greater for reactions of DMAD **40** and PTAD **41** with **52** and **53**. The experimental results differ significantly from the predicted values indicating that product stability is not the predominant factor in determining π-facial selectivity. This is consistent with the irreversibility observed for these reactions. In the case of the reactions with MA **38** and BQ **39**, the "top face" adducts which were formed in negligible amounts are predicted to be produced in 25 - 30% stereochemical yields.

In his study of the reactions of isodicyclopentadiene with various alkene dienophiles, which showed predominantly *endo* facial selectivity, Houk[54] was able to rationalise the experimental results in terms of steric and torsional interactions resulting from bending at the "transition state". His molecular mechanics calculations, based on a fixed model derived from a MNDO calculation for the "transition state" for ethylene and butadiene, were successful in predicting the variation of selectivity with a number of dienophiles. In order to estimate the steric and torsional effects at the transition state, the "transition state" structures arising from reaction from the "top" and "bottom faces" of **52** and **53** with the olefinic dienophiles were modelled using the MMX program. The minimised structure of the product in MMX was transferred to the MODEL program. The carbon atoms involved in the $[\pi 4 + \pi 2]$ framework were replaced by transition state atoms. These structures were then minimised using the transition state MMX force-field parameters.* MMX "transition state" parameters are not available for Diels-Alder reactions involving alkynes and the transition state structures for DMAD reactions were calculated using a "rigid model" developed along the lines of Houk[54] in the recent study of Diels-Alder reactions of **36a** and **36b**.[62]

A summary of the predicted "stabilities" of the "transition state" structures with experimental results is listed in Table 2.4. For the rotationally flexible dienophile DMAD **40**, the MM2 force-field was used and a systematic conformational search was performed

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* The calculations were performed using MMX88 or MMX90 and associated parameters as available from Serena Software, Serena Lane, Bloomington, IN, 47401.

on all the conformationally free bonds in the molecule. The reported results in Table 2.4 for the Diels-Alder reactions with this dienophile are the Boltzmann average energies of the significant lowest energy conformers within 12.6 kJ mol^{-1}.

Table 2.4. Energy differences between transition states ($\Delta E_{(bottom-top)}$, kJ mol^{-1}) calculated using MMX transition state parameters and predicted percentage reaction at the "bottom face" of the Diels-Alder reactions

Dienophiles	**52**			**53**		
	$\Delta E_{(B-T)}$ kJ mol^{-1}	% calcd kJ mol^{-1}	% exp	$\Delta E_{(B-T)}$	% calcd	% exp
MA (**38**)	- 9.1	96	100	- 6.5	90	98
BQ (**39**)	- 7.2	91	95	-	-	-
NQ (**71**)	- 6.8	91	92	-	-	-
DMAD (**40**)[a]	- 20.6	100	20	- 17.9	100	2

[a]Difference is between average Boltzmann energy of significant conformers at 80°C, calculated using a fixed model based on AM1 transition state calculations for acetylene and cyclohexadiene (ref. 62)

With the alkene dienophiles, the MMX total energy of these approximate "transition state" structures predicts a strong preference for formation of the "bottom face" adducts and this is in accord with the experimental observations. Since these calculations take into account only steric and torsional effects, it would appear that the π-facial selectivity of reactions of **52** and **53** with the alkenes can be successfully accounted for by these factors alone. In contrast, for the reaction of DMAD **40** with **52** and **53**, MM TS fixed model calculations predicted formation of 100% "bottom face" adducts while the observed experimental results show a preference for the "top face" adducts. This indicates that, for reactions with alkyne dienophiles, electronic factors are likely to be dominant. Alkyne dienophiles such as DMAD **40** possess filled orbitals which are orthogonal to the forming σ-bonds and may interact repulsively with the lone pair electrons on the acetal and carbonyl moieties of **52** and **53** in attack from the "bottom face", therefore leading to competitive reaction from the "top face".

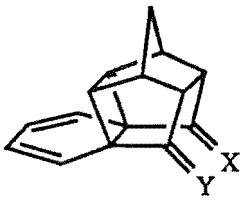
There is no suitable transition state model for reaction of PTAD **41**. A molecular orbital study of the addition of model azo compounds to dienes (cis diimide to butadiene)[93] indicates that the symmetrical "transition state" model may not be an

appropriate model for Diels-Alder reactions with azo dienophiles. Jensen and Foote[94] has proposed a nonconcerted mechanism to account for the results of reactions of PTAD **41** with substituted 2,4-hexadienes.

Chapter 3

Syntheses and Diels-Alder reactions of symmetrically modified cage dienes

Chapter 3 of this thesis describes the syntheses of cage dialkane **103** and dioxime **104** and attempted preparations of monoalkane **105**. Cage dialkane **103** was synthesised for the study of π-facial selectivity in Diels-Alder reactions and represents the crucial case of the "hydrocarbon equivalent" at the atom centers 3 and 10. The elimination of π electrons and oxygen lone pairs on the "bottom face" of the diene in **35**, should allow the importance of these parameters in controlling π-facial selectivity to be determined.



103 X = Y = H_2
104 X = Y = NOH
105 X = H_2, Y = O

Monoalkane **105** would have been an interesting substrate for a π-facial selectivity study as it is equivalent to the intermediate case between the dialkane **103** and diketone **35**, with the reduction of one of the carbonyl groups to an alkane moiety. Unfortunately, various approaches to its formation all failed to produce **105**.

Dioxime **104** is a substrate with both π-electrons and lone pair electrons on nitrogen and oxygen as well as hydroxyl groups. Intermolecular hydrogen bonding between hydroxyl groups strategically substituted on dienes with dienophile carbonyl groups has recently been postulated to control facial selectivity in Diels-Alder reactions.[95]

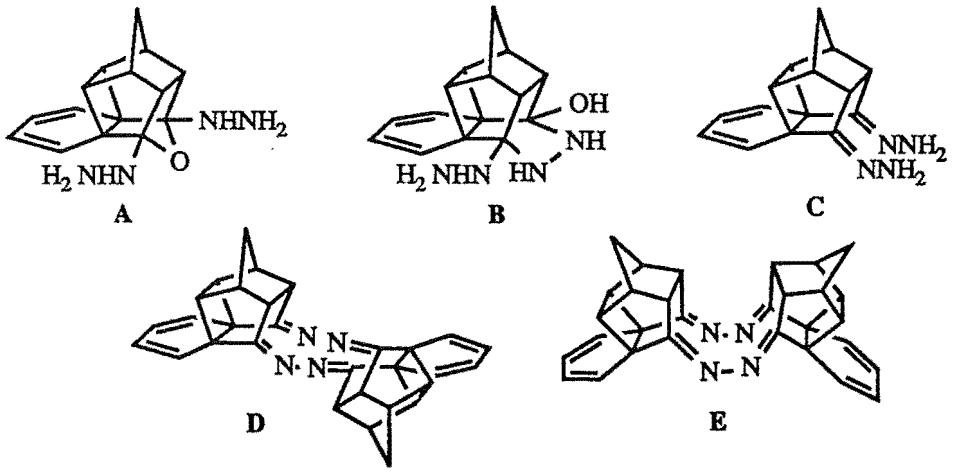
3.1 Syntheses of disubstituted cage diene substrates and associated chemistry of these compounds

3.1.1 Dialkane **103**.

The dialkane **103** was prepared by the modified Wolff-Kishner reduction[76] of the cage diketone **35** where the dihydrazone was generated in situ and decomposed in a one-pot reaction. In contrast to the analogous reaction of pentacycloundecane (PCUD) dione

60 where yields of PCUD of 70% were reported,[76] very low yields (ca. 5%) of dialkane **103** were obtained. Chromatographic separation of the crude product mixture on a silica column yielded a pure sample of the cage dialkane. ^{1}H NMR analysis of this sample showed absorption signals which are comparable with similar cage hydrocarbon compounds.[76] The ^{13}C NMR of **103** showed clearly the absence of the carbonyl signal at 210.4 ppm for C3 and C10 and the appearance of a methylene carbon signal at 33.8 ppm. Various modifications of this reduction procedure, which in related cases were reportedly more effective, were tried. For example the use of the stronger base potassium t-butoxide, in toluene at reflux[96] or in DMSO at room temperature,[97] failed to increase the yield of dialkane. In an attempt to improve the yield, the formation of the dihydrazone from **35** and its subsequent decomposition to dialkane and nitrogen in two separate steps was investigated. Reaction of **35** with excess hydrazine hydrate in toluene at 110°C with azeotropic removal of water with a Dean and Stark trap gave a solid (*ca.* 30%) which precipitated out of the reaction mixture. This was filtered and analysed by ^{1}H NMR, infrared and mass spectroscopy. The infrared spectrum of this solid showed absorption bands at 3280 cm^{-1} and 3220 cm^{-1} but clearly no carbonyl absorption. ^{1}H NMR indicated the presence of two cage dienes, a symmetrical and an unsymmetrical compound in the ratio of 1:3.6. Mass spectrometry showed fragments at 270 a.m.u. and many higher molecular mass fragments up to 539 a.m.u. These results suggest that this solid is a mixture of monomeric and dimeric cage dienes and some of the possible structures **A** - **E** are shown in Chart 3.1.

Chart 3.1

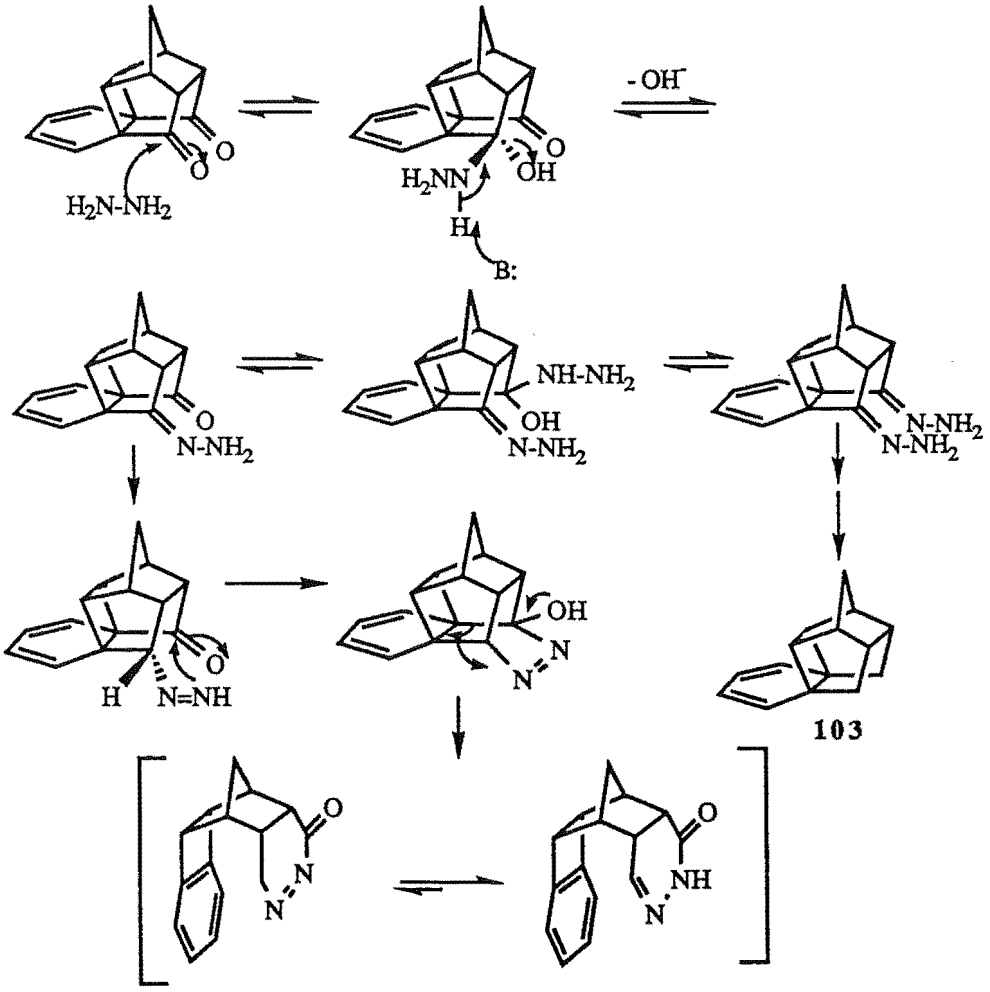


The solvent from the original reaction mixture was removed to give a residue (*ca.* 48%) which was shown to contain only small amounts of the desired dihydrazone. In particular ^{1}H NMR showed the presence of a symmetrical cage diene, infrared spectroscopy showed the absence of a carbonyl group and mass spectrometry showed a low intensity peak at 252 a.m.u. However further reaction of either the solid or the residue in potassium t-butoxide/DMSO gave only small amounts of the dialkane **103**.

The different behaviour of the cage diene **35** in the Wolff-Kishner reaction compared to PCUD dione **60** is due to the presence of the diene moiety. The accepted mechanism for the formation of hydrazones involves firstly nucleophilic attack of hydrazine at the carbonyl center to give a hydroxy-hydrazine adduct which then eliminates water to form the hydrazone [**Scheme 3.1**].[98]

Other potential side reactions such as transannular cyclisation, dimerisation to azines (Chart 3.1) and rearrangement reactions leading to aromatic products (Scheme 3.1;

Scheme 3.1



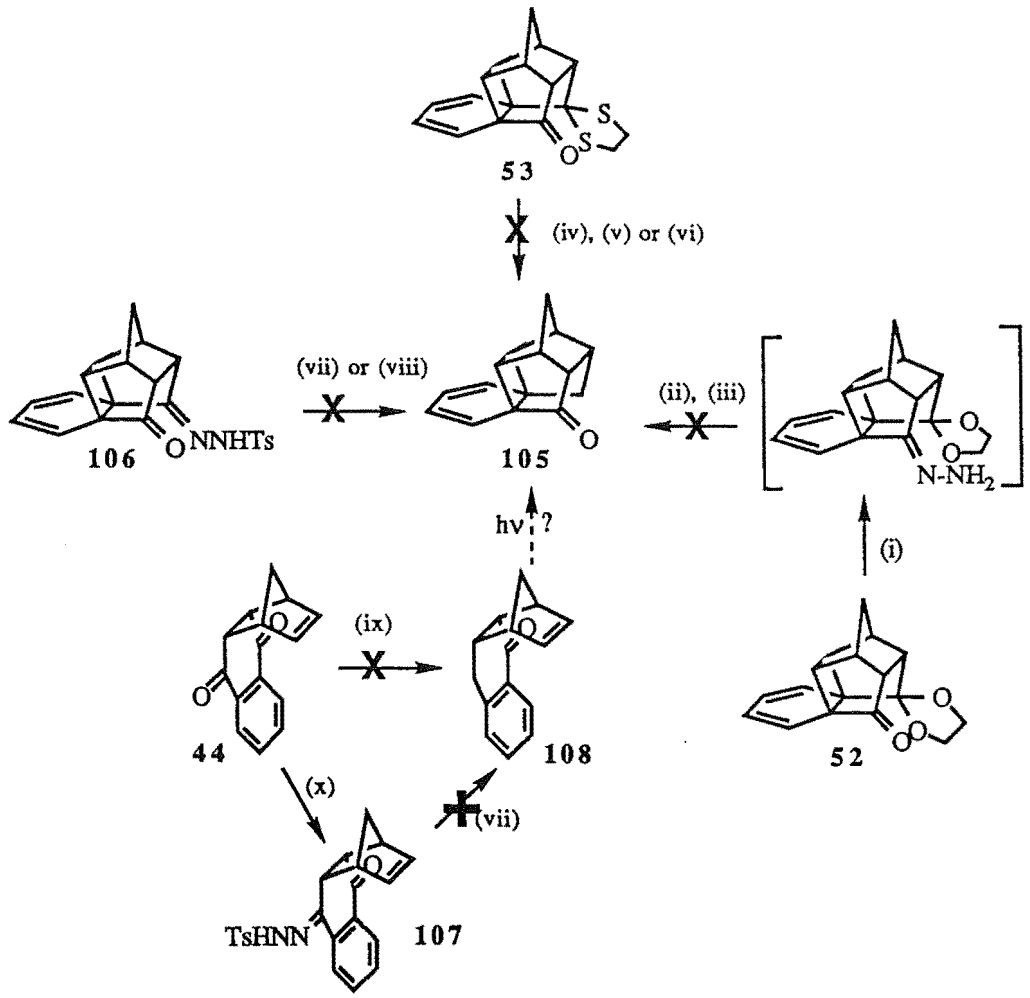
see Chapter 4) can occur in competition to dihydrazone formation and further conversion to dialkane **103**. Despite the low yield, sufficient dialkane **103** was synthesised by the modified Wolff-Kishner procedure for the subsequent Diels-Alder reactions.

3.1.2 Attempted preparation of monoalkane **105**.

Since the attempts at making the dialkane **103** by the modified Wolff-Kishner reduction of diketone **35** met with limited success, the possibility of reducing the mono-protected acetal **52** by the same procedure to give, after deprotection, the monoalkane **105** appeared unattractive and other alternative approaches, as shown in [**Scheme 3.2**], were investigated.

An attempt to prepare the monoalkane cage diene **105** by a two-step procedure involving Clemmensen reduction[99] of the cyclopentadiene-napthoquinone adduct **44** with

Scheme 3.2



(i) Hydrazine hydrate/ethanol/reflux (ii) Potassium t-butoxide/DMSO (iii) H^+/THF
(iv) Raney-Nickel/ethanol (v) $CuCl_2/ZnCl_2/LiAlH_4$ (vi) Hydrazine/diethyleneglycol (vii) $NaBH_4$/methanol
(viii) $NaBH_3CN$/DMF/sulfolane (ix) Zn/HgCl (x) p- Tosylsulphonyl hydrazine/glacial acetic acid

Zn/HCl followed by photoclosure of **108** was unsuccessful. Instead of forming **108**, the compound **44** appeared to undergo a retro-Diels-Alder reaction.

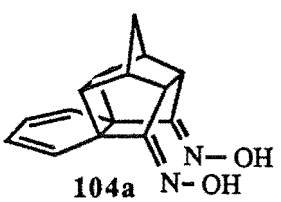
Reaction of **44** with one molar equivalent of p-toluenesulphonyl hydrazine gave a mixture of dihydrazone and monotosylhydrazone **107** which was purified by chromatography. However, reduction of **107** with sodium borohydride in methanol did not yield **108**.

Desulphurisation of the thioacetal **53** with Raney nickel catalyst resulted in an intractable mixture and from the ^{1}H NMR spectrum of the mixture it was apparent that the diene moiety had undergone reduction. An alternative attempt at desulphurisation using a mixture of $CuCl_2/ZnCl_2/LiAlH_4$, which has been reported to reduce thioacetals in the presence of olefinic bonds,[100] did not affect the cage diene but was also not successful in reducing thioacetal **53**. Another desulphurisation method which employs hydrazine hydrate in diethyleneglycol[101] was also tried without success.

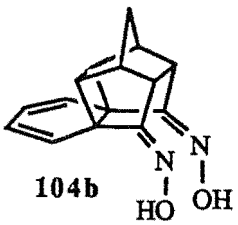
Reaction of cage diketone **35** with 1 molar equivalent of p-toluenesulphonyl hydrazine gave the monotosylhydrazone **106** in quantitative yield. However, reduction of **106** with either sodium borohydride in methanol[102] or sodium cyanoborohydride in dimethylformamide/sulfolane[103] did not result in the reduction of the tosylhydrazone moiety (see Chapter 4).

3.1.3 Dioxime **104**.

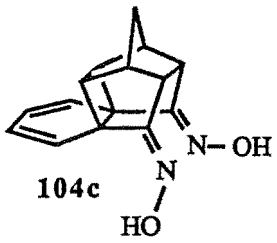
Reaction of cage diketone **35** with hydroxylamine[74] proceeded smoothly to form, in 77% yield, the dioxime **104** which can exist as three geometrical isomers **104a** - **104c**. ^{1}H NMR and ^{13}C NMR analysis of the product at room temperature was in accord with a cage structure with mirror symmetry. Thus the unsymmetrical isomer



104a



104b



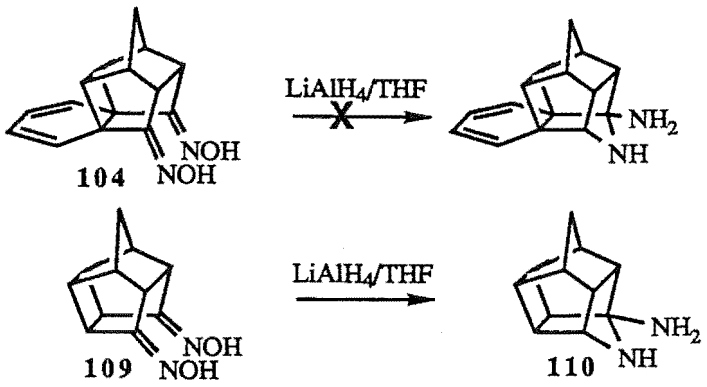
104c

104c can be eliminated. Molecular mechanics calculations (MMX) on structures **104a**, **104b** and **104c** indicated that, based solely on steric grounds, dioxime **104a** is the most

stable. However the MMX mean energy difference between **104a** and **104b** is only 5.9 kJ mol^{-1}.†

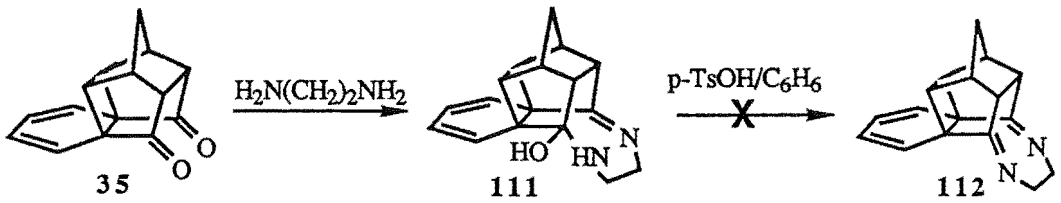
The contrasting behaviour of this hexacyclic cage diene compared to the PCUD series is seen in the attempted reduction of the dioxime **104** with lithium aluminium hydride/THF wherein an intractable mixture was obtained, whereas in the case of the corresponding PCUD dioxime **109** the cyclic amine **110** was formed [**Scheme 3.3**].[74]

Scheme 3.3



Attempts to prepare diimine analogues of the cage diketone were made by reacting cage diketone **35** with aniline, benzylamine, o-phenylenediamine and 1,2-ethanediamine. All these reagents gave complex mixtures except for 1,2-ethanediamine where the monoimine **111** was formed. Attempts to dehydrate **111** to the diimine **112** were not successful [**Scheme 3.4**].

Scheme 3.4



3.2 Diels-Alder reactions of 103 and 104

Addition reactions were carried out with representative dienophiles selected from the alkene, alkyne and azo classes. Product ratios were determined by 300 MHz ^{1}H NMR spectral analysis of crude reaction mixtures and are summarised in Table 3.1. The stereochemistries of the adducts were determined mainly by nuclear Overhauser effect difference spectroscopy (NOED) on the purified products as described previously.

† Based on this energy difference, the predicted Boltzmann distribution of the two isomers **104a** to **104b** is 87%:13% at 78 °C.

Table 3.1. Product Ratios[a] for the Diels-Alder reactions[b] of dialkane **103**, dioxime **104**, **35**[58], **36a** and **36b**.[62]

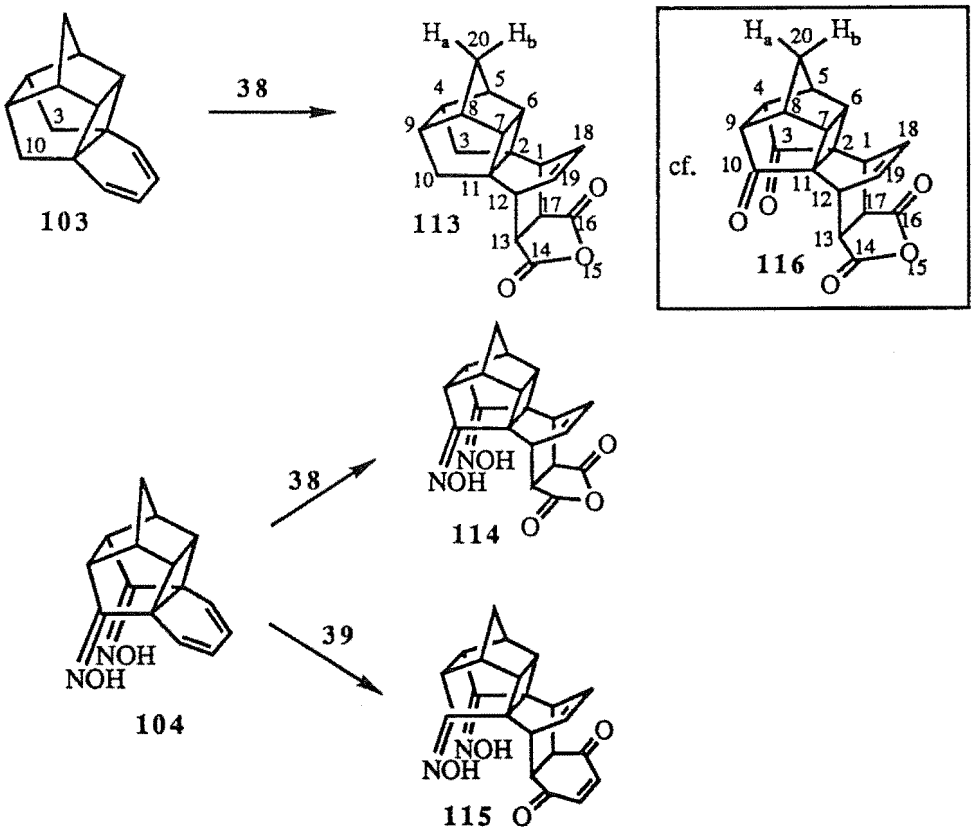
Dienophile	% reaction at the "bottom face" of the diene				
	103	**104**	**35**	**36a**	**36b**
MA (**38**)	100	100	100	100	85
BQ (**39**)	-	100	100	100	100
DMAD (**40**)	100	-[c]	55	25	10
PTAD (**41**)	100	87	64	78	93

[a]Product ratios (± 2%) from 300 MHz ^{1}H NMR analysis of crude reaction mixtures.
[b]All reactions were conducted in benzene at 80°C except for reactions involving PTAD 41 which were conducted in dichloromethane at 0-5°C.
[c]Decomposition after heating the reaction mixture at 80°C for 7 days.

3.2.1 Reactions with alkene dienophiles

The π-facial selectivities in reactions of dialkane **103** and dioxime **104** with the alkene dienophiles, maleic anhydride (MA, **38**) and p-benzoquinone (BQ, **39**), are similar to those of the diketone **35**, i.e. attack of the dienophiles from the "bottom face" of these dienes leads to exclusive formation of only one diastereomeric adduct **113** - **115** [**Scheme 3.5**].

Scheme 3.5



The chemical shifts of the ^{1}H NMR and ^{13}C NMR spectra of **113** and the other dialkane adducts are strikingly different from their analogues from the corresponding diketone **35** series, which exhibit orbital interactions with the carbonyl groups at atom centers 3 and 10 [**Tables 3.2(i)** and **3.2(ii)**].[104] The protons on the norbornyl moiety show upfield shifts of *ca.* 0.3 ppm to 0.7 ppm, e.g. H6 and H7 in **113** resonate at 2.02 ppm compared to 2.72 ppm in the diketone-MA adduct **116**. The ^{13}C NMR chemical shift value for C6 and C7 in **113** is 4 ppm downfield at 45.2 ppm (cf. 41.6 ppm in the diketone-MA adduct **116**). These remote substituent effects are due to orbital mixing of the carbonyl and cyclobutane C-H orbitals.[62,104] The carbon centers adjacent to the C3 and C10 centers, viz C4 and C9, experience an upfield shift of 10 ppm from 55.9 ppm in the diketone-MA adduct **116** to 46.1 ppm in **113**. This is due to the inductive effect of the electron withdrawing carbonyl group in the diketone-MA adduct **116**.

Unlike the dimethylidene cage diene **36b** where the geometry of the exocyclic methylene protons is such that they provided a greater steric barrier to reaction at the "bottom face", the protons at the methylene C3, C10 centers in **103** provide no such impediment. This is reflected in the 100% "bottom face" selectivity of MA **38** for **103** compared to **36b** where only 85% of the "bottom face" adduct was observed.[62]

Diene **104** was relatively unreactive. Reaction of MA **38** or BQ **39** with **104** gave only "bottom face" adduct(s) **114** and **115** respectively. The reactions were stopped prematurely as, on further reflux, isomerisation of the oxime moiety was observed.

3.2.2 Reaction with dimethylacetylene dicarboxylate (DMAD, **40**).

DMAD **40** reacted with dialkane **103** with exclusive selectivity for the "bottom face" leading to the formation of a single adduct **117** [**Scheme 3.6**]. The stereochemistry of this adduct was confirmed by the mutual nuclear Overhauser enhancements of the cyclobutane ring protons with the olefinic protons and also by an X-ray crystal structure determination. Figure 3.1 shows a perspective view of the crystal structure of this adduct.

Table 3.2(i). Comparison of ^{1}H NMR chemical shift values of dialkane-MA adduct **113** with diketone-MA adduct **116**.[a]

Proton	^{1}H NMR δ (ppm)		
	113	**116**	Difference in δ value[b] (ppm)
$H3_a$, $H10_a$	1.09	-	-
$H3_b$, $H10_b$	1.34	-	-
$H20_b$	1.12	1.86	-0.74
$H20_a$	1.57	2.02	-0.45
H6, H7	2.02	2.72	-0.70
H4, H9	2.30	2.79	-0.49
H5, H8	2.30	2.95	-0.65
H1, H12	3.02	3.36	-0.34
H13, H17	3.13	3.77	-0.64
H18, H19	6.44	6.50	-0.06

[a] ^{1}H NMR δ values and assignment for diketone-MA adduct **116** are from ref 58.
[b] A positive value denotes a downfield shift (increase in δ value).

Table 3.2(ii). Comparison of ^{13}C NMR chemical shift values of dialkane-MA adduct **113** with diketone-MA adduct **116**.[a]

Carbon	^{13}C NMR δ (ppm)		
	113	**116**	Difference in δ value[b] (ppm)
C3, C10	29.7	211.0	-
C20	34.5	40.8	-6.3
C1, C12	38.4	32.6	5.8
C5, C8	41.4	43.6	-2.2
C13, C17	42.2	39.5	2.7
C6, C7	45.2	41.6	3.6
C4, C9	46.1	55.9	-9.8
C2, C11	48.9	52.8	-3.9
C18, C19	133.2	132.9	0.3
C14, C16	173.2	172.1	1.1

[a] ^{13}C NMR δ values and assignment for diketone-MA adduct **116** are from ref 58.
[b] A positive value denotes a downfield shift (increase in δ value).

Scheme 3.6

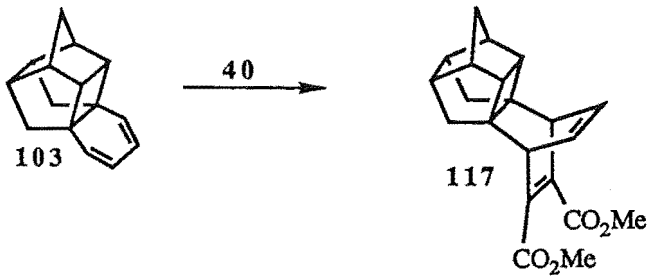
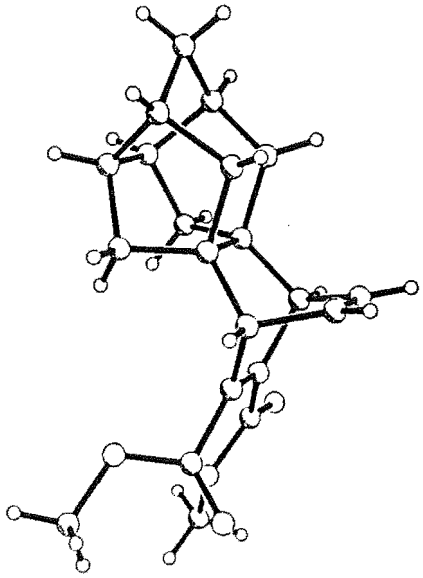


Figure 3.1. X-Ray Structure of **117**



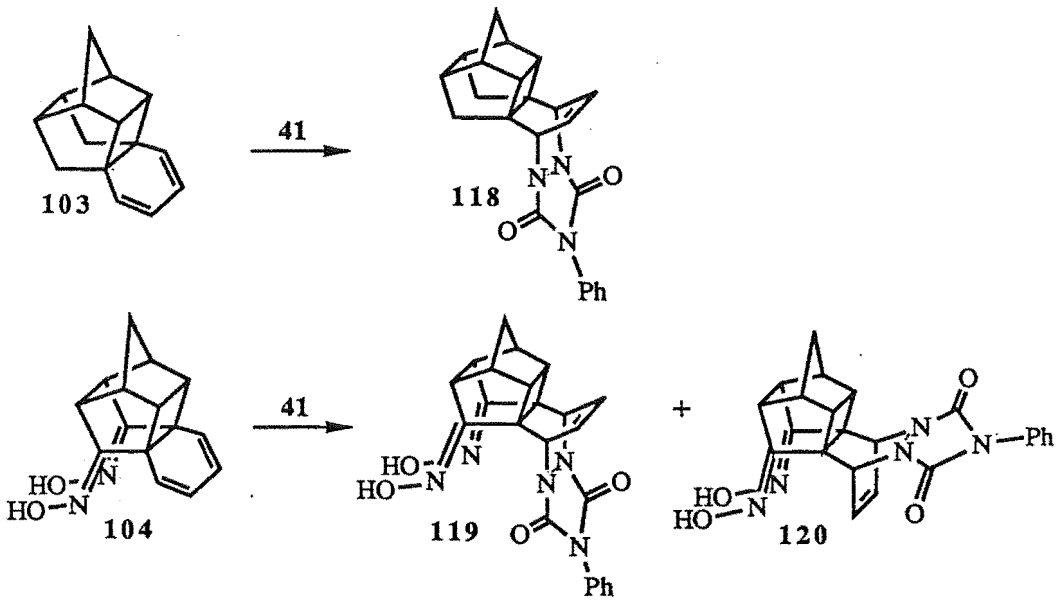
The contrasting behaviour of DMAD **40** with dialkane **103** compared to diketone **35** where 45% of the corresponding "top face" adduct was formed clearly shows the importance of the π electrons and oxygen lone pairs at atom centers 3 and 10 in determining π-facial selection in these Diels-Alder reactions.

The dioxime **104** was very unreactive and relatively unstable. Indeed prolonged reflux with DMAD at 80°C over 7 days led to the decomposition of the starting materials.

3.2.3 Reactions with N-phenyltriazoline dione (PTAD, **41**)

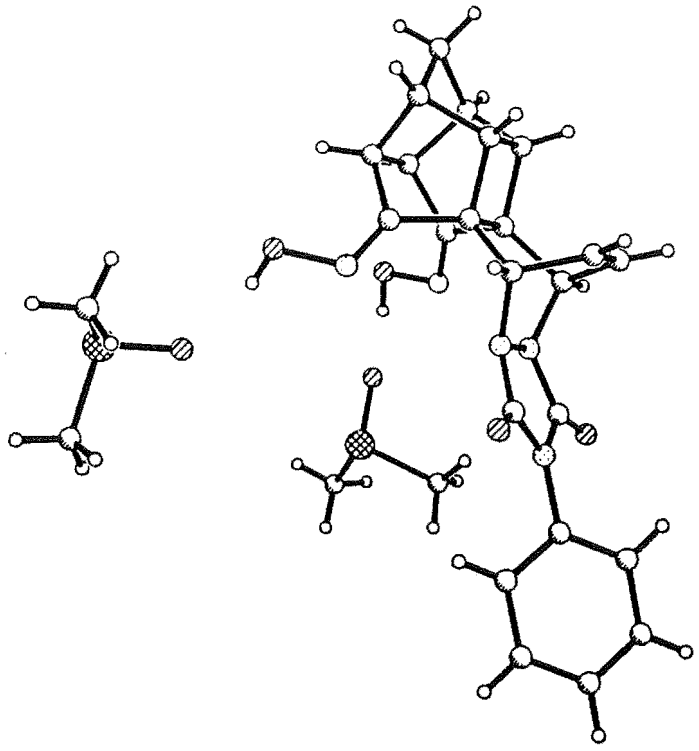
Reaction of PTAD **41** with dialkane **103** gave exclusively the "bottom face" adduct **118** [**Scheme 3.7**]. This also differs from diketone **35** where 36% of "top face" addition was observed and further supports the theory that the oxygen lone pairs of **35** repel incoming acetylene and azo dienophiles.[58]

Scheme 3.7



Reaction of PTAD **41** with dioxime **104** showed a high selectivity for the "bottom face" of the diene, producing 87% of **119**, compared to 64%, 78% and 93% of the corresponding adducts for the reactions of this azo dienophile with **35**, **36a** and **36b** respectively [**Scheme 3.7**]. The stereochemistries of the adducts are supported by NOED experiments and, in one case, was confirmed by an X-ray structure determination of a DMSO solvate of **119** [**Figure 3.2**].

Figure 3.2. X-Ray Structure of **119**



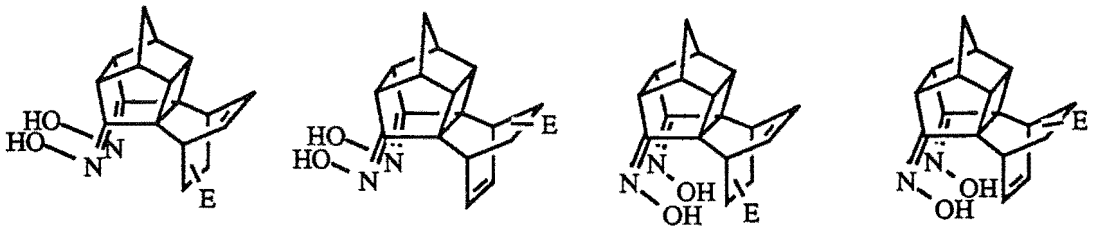
Furthermore, this structural study revealed that the hydroxyl groups of the oxime moieties are positioned anti to the cyclobutane ring. The hydroxyl groups would have to be positioned syn to the cyclobutane ring in order to be involved in intermolecular hydrogen bonding with the carbonyl oxygen or azo nitrogen of PTAD **41** in the Diels-Alder "transition state" structures. Therefore, the evidence militates against the involvement of hydrogen bonding in determining π-facial selectivity in these reactions.

3.3 Molecular mechanics calculations (MMX)

Force field calculations (MMX) were performed on the products and "transition state" structures of the reactions of dialkane **103** with MA **38**, DMAD **40** and PTAD **41** [**Tables 3.3** and **3.4**]. Table 3.3 shows that the predicted product stabilities of the adducts are not in good agreement with the experimentally observed π-facial selectivities of these Diels-Alder reactions. Therefore, product stability is not a determining factor in the facial selection in these reactions.

The agreement between predicted and observed product ratios is considerably improved for the case of TS (MMX) calculations on the MA adducts and the MM (TS) "fixed model" calculations on the DMAD adducts [**Table 3.4**]. Hence, a "steric only" model of the "transition state" structures adequately accounts for the percentages of the adducts formed.

Molecular modelling (MMX) of the 4 possible adducts **A** - **D** formed from the reaction of dioxime **104** with each of the dienophiles, MA **38**, BQ **39** and PTAD **41** showed that the total steric energies of structures **C** and **D** are higher relative to those of **A** and **B**, typically by 16 kJ mol^{-1}, and therefore would be expected to contribute little to the Boltzmann distribution of the isomers (i.e. <<0.1%).



A **B** **C** **D**

Tables 3.3 and **3.4**, show that both the MMX (product) and MMX (TS) calculations successfully predicted the exclusive formation of the "bottom face" adducts

for the reaction of dioxime **104** with MA **38** and BQ **39** In these reactions, a "steric only" model of the products and "transition state" structures leading to the adducts successfully predicted the π-facial selectivities and it is likely that steric effects are the dominant factor involved.

Table 3.3. Calculated (MMX) energy differences ($\Delta E_{(bottom - top)}$, kJ mol^{-1}) between adducts resulting from "bottom face" and "top face" reaction ($\Delta E_{(B-T)}$) and calculated percentage "bottom face" reaction at 80°C (% calcd) of dialkane **103** and dioxime **104** with selected dienophiles compared with experimental result (exp).

Dienophiles	Dialkane **103**			Dioxime **104**		
	$\Delta E_{(B-T)}$ kJ mol^{-1}	% calcd	% exp	$\Delta E_{(B-T)}$ kJ mol^{-1}	% calcd	% exp
MA (**38**)	- 5.2	86	100	-38.1	100	100
BQ (**39**)	-	-	-	-27.5	100	100
DMAD (**40**)[a]	- 0.5	55	100	-	-	-
PTAD (**41**)[b]	1.2	38	100	-47.1	100	87

[a]Calculated using BAKMDL (MM2) energy difference between the average energy of significant conformers at 80°C.
[b]Calculated at 0°C.

Table 3.4. Energy differences between transition states ($\Delta E_{(bottom-top)}$, kJ mol^{-1}) calculated using MMX transition state parameters and predicted percentage reaction at the "bottom face" of the Diels-Alder reactions

Dienophiles	Dialkane **103**			Dioxime **104**		
	$\Delta E_{(B-T)}$ kJ mol^{-1}	% calcd	% exp	$\Delta E_{(B-T)}$ kJ mol^{-1}	% calcd	% exp
MA (**38**)	- 10.6	97	100	-18.8	100	100
BQ (**39**)	-	-	-	-21.2	100	100
DMAD (**40**)[a]	- 16.8	100	100	-	-	-

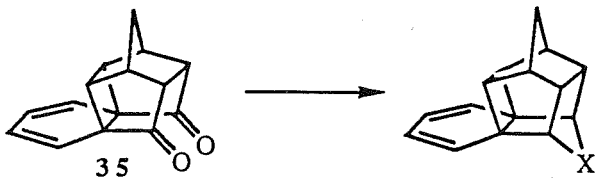
[a]Difference is between average Boltzmann energy of significant conformers at 80°C, calculated using a fixed model based on AM1 transition state calculations for acetylene and cyclohexadiene (ref 62).

Chapter 4

Syntheses, incidental chemistry and Diels-Alder reactions of bridged cage dienes

The syntheses, incidental chemistry and subsequent Diels-Alder reactions of some transannular bridged dienes **121** - **123** will be discussed in the fourth chapter of this thesis. The attempted syntheses of **124** and **125** will also be reported [**Scheme 4.1**].

Scheme 4.1



121 X = O
122 X = - OCH_2O -
123 X = - $OC(CH_3)_2O$ -
124 X = NH
125 X = S

The dienes **121** - **125** possess oxygen, nitrogen or sulfur lone pairs proximate to the diene moiety but do not possess the exocyclic π electrons such as in **35**, **36a** and **36b**. Such cage dienes which are bridged by a heteroatom such as oxygen would have the ether oxygen placed centrally between C3 and C10. In this location the lone pair electrons of the oxygen would be fixed by the rigid cage structure and would be positioned to interact with dienophiles attacking the diene from the "bottom face". Moreover, the overall geometry of the cage ether **121** is expected to be similar to the cage diketone **35**; hence this substrate should offer similar steric effects in Diels-Alder reactions.

The cyclic acetal **122** is a substrate in which the two oxygen atoms are positioned between the oxygens of the diketone **35** and the oxygen of the cage ether **121**. However in compound **122**, unlike **35**, the acetal moiety does not contain π electrons. Hence, the effect of the oxygen lone pair electrons in this configuration, on π-facial selectivity can be studied independently of the contribution of π electrons.

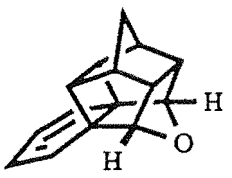
The diene **123** in which the C3 and C10 in diketone **35** is bridged by an acetonide group should be somewhat similar to **122** in the placement of the oxygen groups. However, the dimethyl moiety will provide steric hindrance towards dienophiles reacting from the "bottom face" of the diene.

In an effort to investigate the effect of variation of the heteroatom X on facial selectivity, attempts were made to prepare the bridged amine **124** and sulphide **125**. These proved to be unsuccessful but some interesting chemistry was encountered.

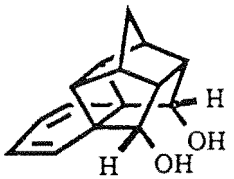
4.2 Syntheses and incidental chemistry of bridged cage compounds

4.1.1 Cage ether **121**.

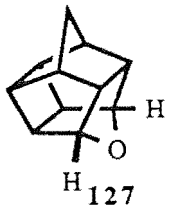
The attempted preparations of the cage ether **121**, by dehydration of the *endo-endo* diol **126**, again highlight the differing chemistry of these hexacyclic cage compounds compared with the closely related PCUD cage compounds. The ether **127** is readily prepared from the pentacyclic diol **128** by a variety of methods in 60 - 90% yields; indeed, this reaction was used as evidence for the *endo-endo* configuration of the diol. In contrast, the hexacyclic diol **126** proved remarkably resistant to dehydration under a variety of conditions that effect the conversion of **128** to **127**. Thus reaction of **126** with p-TsOH at 25°C[71] or 80°C,[105] conc. H_2SO_4,[106] 48% HBr,[107] P_2O_5/Δ, p-TsCl[72] or thermolysis at 220°C[64] all resulted in either the recovery of the starting diol or products of rearrangement or polymerisation.[93,108]



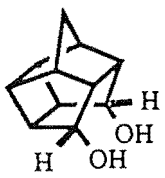
121



126



127

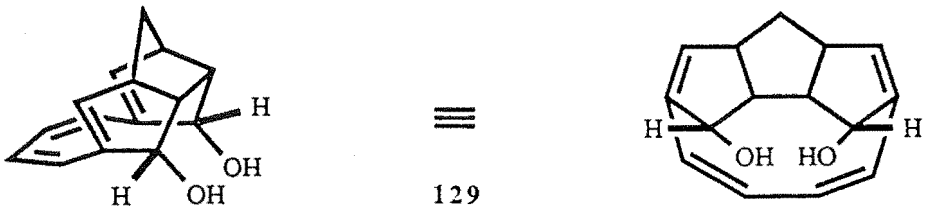


128

The different behaviours of **126** and **128** towards dehydrating agents must be associated with the presence of the additional cyclohexadienyl ring, which induces only small structural changes at the reacting hydroxyl centres. However molecular mechanics calculations† for each compound indicate that there are only small differences in the geometries of the two centres and these are unlikely to be responsible for the differences in reactivity with respect to dehydration. It is more likely that the diene moiety in **126** provides alternative pathways for rearrangements leading to aromatic products once substantial positive charge develops in the course of acid- or thermally- induced loss of

† The calculations were performed using MMP2 force field as implemented in BAKMDL (1991) to allow for conformational searching of the hydroxyl groups. The average distance between the reaction centers of the significant conformers of diol **126** and PCUD diol **128** is 2.904Å and 2.902Å.

the homoallylic hydroxyl group. Indeed acid-catalysed rearrangements of related dienes to aromatic products have previously been reported.[80,109] In fact, an effort to prepare **123** by p-toluenesulphonic acid catalysed acetalisation reaction of the *endo-endo* diol **126** with acetone under forcing conditions, i.e. reflux at 80°C for 60 hours with azeotropic removal of water/benzene, resulted in the formation of the cage ether **121** along with aromatic product(s) and acetonide **123**§. In addition other modes of rearrangement are available to the diol. For example, during the course of chromatography of diol **126** on silica gel, O'Connell observed some rearrangement of **126** to the diene-bridged triquinane **129**.[108] This [$_{\sigma}2 + _{\sigma}2$] cycloreversion is analogous to that observed by Mehta[110] from flash vacuum pyrolysis of a related diketone.



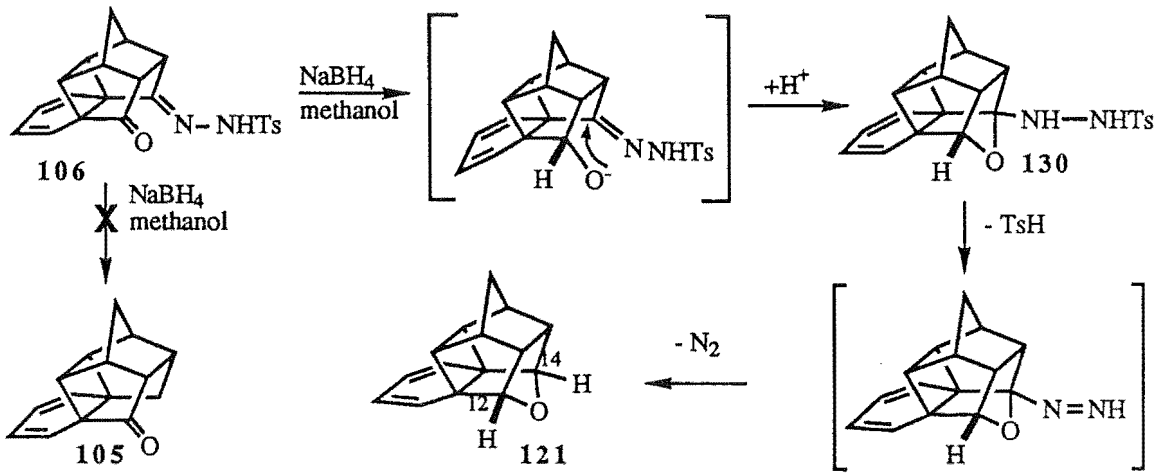
129

As described earlier a supply of the monohydrazone **106** was required for the attempted preparation of the monoalkane **105** by reduction.[102] The monohydrazone **106** was formed in quantitative yield by reacting the cage diketone **35** with one molar equivalent of p-tosylhydrazine in glacial acetic acid [**Scheme 4.2**].[111] Subsequent reduction of **106** with sodium borohydride in methanol for nine days gave a mixture of the tosylhydrazine **130** (60%) and the ether **121** (20%). Scheme 4.2 shows a mechanism for the formation of these products which involves initial reduction of the carbonyl group, followed by transannular cyclisation, conversion to the hydrazoether and loss of nitrogen.

The intermediacy of the hydrazine **130** in the formation of **121** was confirmed by its separate conversion to the ether **121** under the same reaction conditions but for a longer reaction period. This in turn improves the overall yield of the ether and made available sufficient quantities of this diene for studies of the π-facial selectivities of its Diels-Alder reactions. This reaction sequence again represents a change in chemistry as a

§ In the absence of acetone, dehydration of diol **126** also occurred and the cage ether **121** (20% as estimated by ^{1}H NMR), aromatic rearrangement product(s) and unreacted diol **126** were obtained.

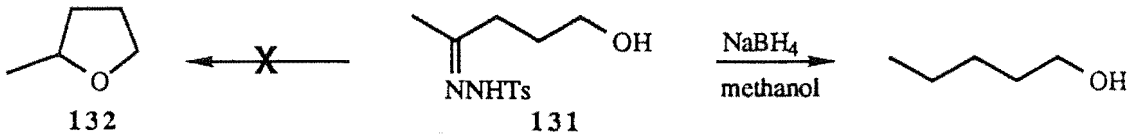
Scheme 4.2



consequence of the additional cyclohexadienyl ring since the related monotosylhydrazone which lacks this ring has recently been shown by Marchand to react with sodium borohydride to give a hexacyclic azoalkane.[114b]

In order to assess whether this might be a general procedure for the preparation of cyclic ethers, the hydroxy-tosylhydrazone **131** (as a mixture of geometrical isomers) was reacted with sodium borohydride under the same reaction conditions. This produced pentanol as the only product, by the standard reduction reaction of tosylhydrazones,[102] and none of the cyclic ether **132** [**Scheme 4.3**], which would result from an analogous reaction to that described above. Thus the formation of the cyclic ether **132** relies on the close proximity of the oxygen to the transannular carbon, a factor that is responsible for much of the interesting chemistry observed in such cage compounds.[75]

Scheme 4.3

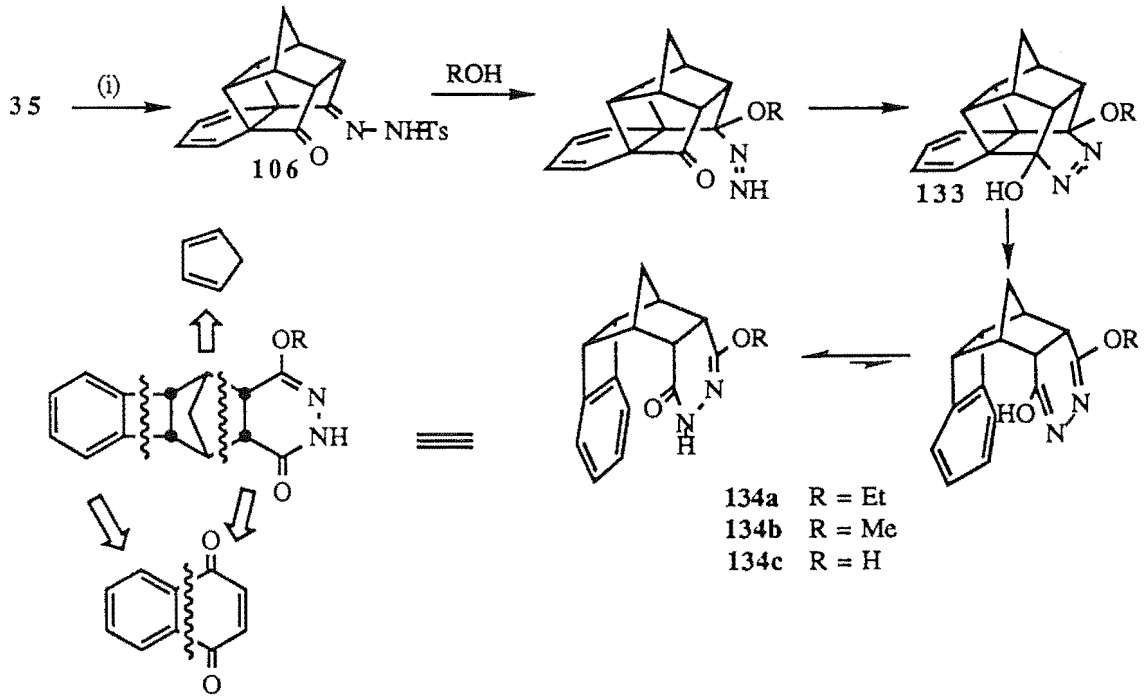


The ^{1}H NMR and ^{13}C NMR of the cage ether **121** are consistent with the assigned structure which possesses mirror symmetry. This is indicated from the appearance of the ^{1}H NMR spectrum and the eight non-equivalent carbon signals in the ^{13}C NMR spectrum. The bridged nature of the compound is evident from the proton signal of the *exo* hydrogens, H12 and H14, which resonate as a triplet at δ 4.50 ppm; the chemical shift and splitting pattern are typical of *exo* hydrogens of bridged cage compounds.[112]

The ^{13}C NMR resonance signal for C12 and C14 is at 92.1 ppm which is also consistent with an oxygen bridge between these centers.

In the course of preparing a supply of the tosylhydrazone **106**, we observed that **106** undergoes a novel rearrangement to the pentacyclic pyridazine derivative **134a** on reaction with alcohols [**Scheme 4.4**].[113] In our first attempts to prepare tosylhydrazone **106**, reaction of **35** with one equivalent of p-tosylhydrazine in refluxing ethanol[111] for 30 min gave the expected monohydrazone **106** as a minor (15%) product along with a rearranged product subsequently identified as **134a** (85%). The smooth conversion of **106** into **134a** and **134b** in refluxing ethanol and methanol† respectively demonstrated that **134a** was a secondary product.

Scheme 4.4

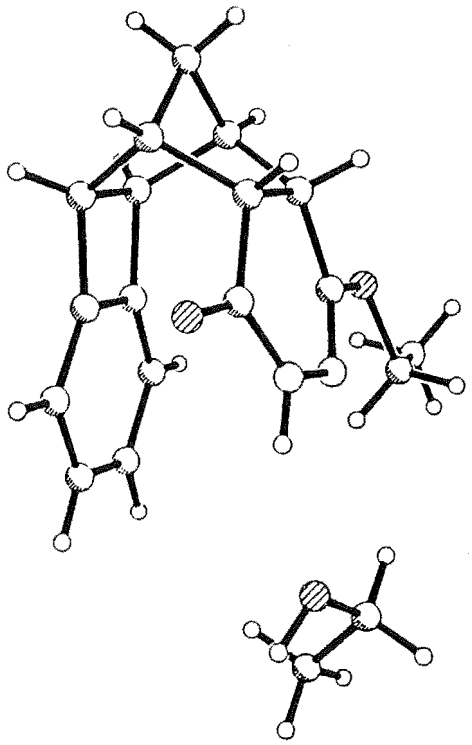


The structural identity of **134a** was deduced from its spectroscopic properties; in particular the NMR spectra indicated the presence of an ortho-disubstituted benzene ring and a tetra-*endo*-substituted norbornane skeleton. The structure was confirmed by a single crystal X-ray structure determination of the ethanol solvate of **134a**. Figure 4.1 shows a perspective view of the structure. The fusion of a benzocyclobutene to the norbornane skeleton results in an elongation of the C2-C9 bond. The structure is of

† On standing the hydrazone **106** slowly undergoes hydrolytic rearrangement to the corresponding hydroxy derivative **134c** (R = H).

particular interest because of the way in which the norbornane skeleton enforces a cofacial orientation of the benzene and pyridazine rings, their meanplanes being approximately coplanar (16°) and separated by ca. 3 Å. As a result the molecule contains a molecular cleft which has potential to act as a host for inclusion compounds.

Figure 4.1. X-ray structure of **134a**.

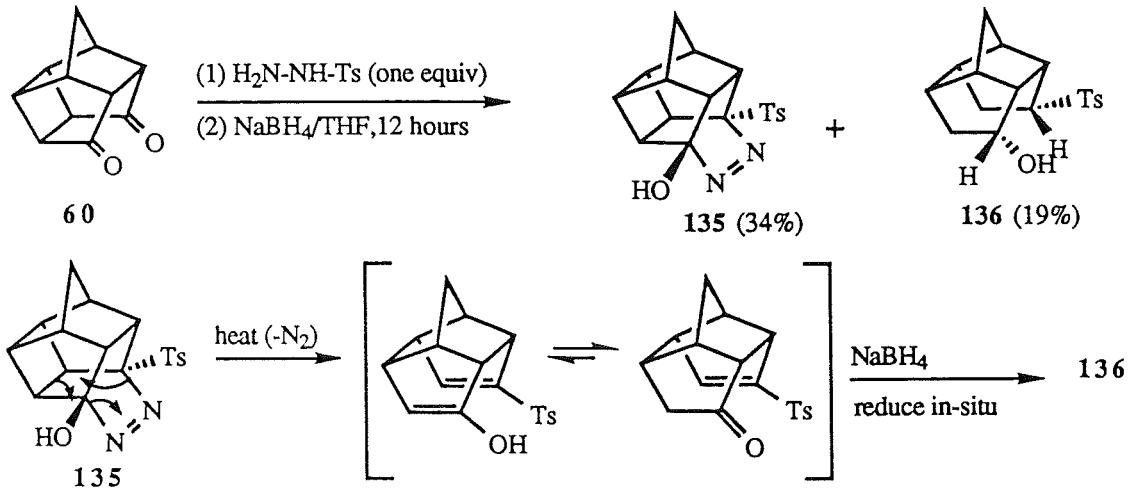


The conversion of **106** to **134** is considered to involve a $[_{\pi}4 + _{\pi}2]$ cycloreversion of the heptacyclic intermediate **133**, a process driven by aromatisation [**Scheme 4.4**]. This rearrangement represents a new fragmentation pathway for the PCUD skeleton and involves double α-cleavage of the precusor. A photoinduced double β-cleavage of **35** has recently been claimed.[114a] The structure of the carbon skeleton of **134** is of interest when one considers the origin of the component fragments; the reaction sequence leading to **134** formally corresponds to the insertion of cyclopentadiene between the rings of the naphthoquinone precursor.

This rearrangement pathway is attributed to the relative ease of the cyclohexadienyl unit to reform the benzylic ring which was destroyed on photocycloaddition of the *endo*-naphthoquinone-cyclopentadiene adduct to form **35**. Marchand et al. have recently reported a similar reaction of the related PCUD dione **60** [**Scheme 4.5**].[114b] In their case, the cyclic azo alkane intermediate **135**, which is apparently more stable than the

corresponding analogue **133**, was isolated in 34% yield. In the absence of the cyclohexadienyl unit, thermally induced rearrangement of this intermediate led instead to the extrusion of nitrogen followed by the in-situ reduction of the corresponding intermediate to form **136** [**Scheme 4.5**].

Scheme 4.5

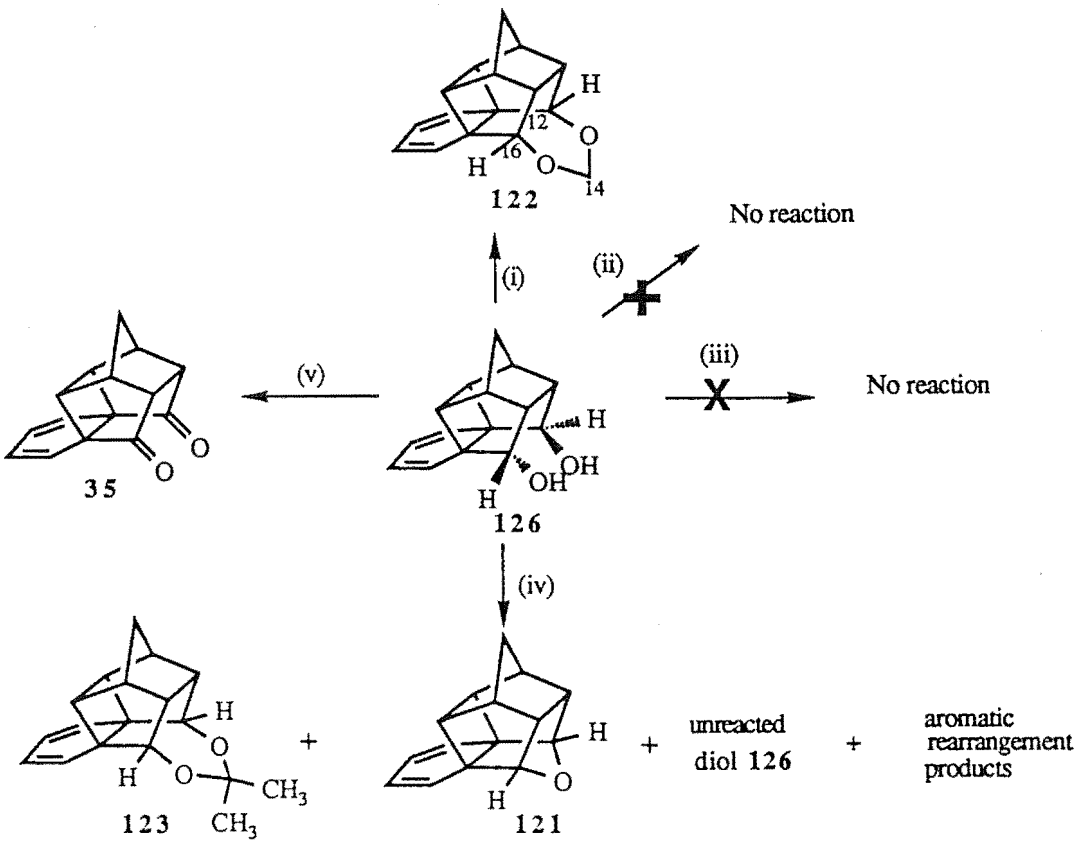


4.1.2 Cyclic acetal **122**.

Cyclic acetals are readily obtained by acid catalysed reactions of diols with formaldehyde since acetalisation involving 5- or 6-membered ring formation is favoured compared with an acyclic case.[115] Diol **126** was prepared by the reduction of diketone **35** with sodium borohydride in methanol to give a mixture of the *endo-endo* diol **126** (80%) and *endo-exo* diol (20%). Addition of cerium trichloride to the reduction mixture did not improve the facial stereoselectivity of the reduction as was reported for PCUD dione **60**.[71]

As the geometry of the *endo-exo* diol is such that cyclic acetal formation would not be favoured, the crude reaction mixture of the two diols was used without purification for the subsequent reaction . This mixture of diols was reacted with formalin in benzene and the reaction was catalysed by p-toluenesulphonic acid. Water was removed as an azeotrope with benzene. This reaction gave the cyclic acetal **122** (66%) and the unreacted *endo-exo* diol which was easily separated from the acetal **122** by chromatography as these compounds have quite different R_f values on silica [**Scheme 4.6**].This procedure also provides an easier method of purifying the *endo-exo*-diol as the previously reported purification[108] involved repeated recrystallisation of the mixture of diols.

Scheme 4.6



(i) formalin (40% soln), p-TsOH, benzene (- H_2O) reflux 3 hours
(ii) acetone, p-TsOH ,3A or 4A molecular sieves (remove water), reflux 36 hours
(iii) acetone, BF_3, room temperature, 5 days
(iv) acetone, p-TsOH, benzene (- H_2O), reflux, 60 hours
(v) acetone, $FeCl_3$, reflux 24 hours.

The structure of the acetal **122** was confirmed from the mirror symmetry evident in ^1H NMR and ^{13}C NMR spectra. The presence of nine non-equivalent carbon signals in its ^{13}C NMR spectrum is consistent with this structure. Chemical shifts and splitting patterns of key NMR signals, such as the protons H12 and H16 [δ 3.89 (t, 2H)], the acetal methylene protons H14 [δ 4.86, 4.91 (AB-q, J = 7.0 Hz)] and the carbon signals at these centers [δ 83.8 (C12,C16); 90.5 (C14)], are all consistent with the assigned structure.

Formally, the cyclic acetal moiety in **122** corresponds to a 7-membered acetal ring, the formation of which would normally not be favourable. However, the rigidity of the cage structure circumvents this problem by bringing the reacting centers into proximity, and the geometry of the cyclic acetal moiety is in reality more akin to a 5- membered ring acetal.

4.1.3 Acetonide **123.**

Attempts to prepare the acetonide **123** by the reaction of *endo-endo* diol **126** with acetone (i) catalysed by p-toluenesulphonic acid with 3A or 4A molecular sieves at room temperature and under reflux conditions,[116] (ii) catalysed by boron trifluoride at room temperature for 5 days,[117] and (iii) catalysed by ferric chloride[118], were all unsuccessful. They resulted in either the recovery of the diol or, in the case of catalysis with ferric chloride, oxidation of the diol back to the diketone **35**. Reaction of the diol **126** with acetone, in the presence of p-toluenesulphonic acid in benzene for 60 hours, with azeotropic removal of water using a Dean and Stark trap resulted in a mixture of the acetonide **123**, unreacted diol **126**, cage ether **121** and aromatic rearrangement product(s) in a ca. 2:2:1:1 ratio [**Scheme 4.6**]. Attempts at purifying the mixture by chromatography on silica were unsuccessful as the acetonide **123**, ether **121** and aromatic product(s) all have very similar R_f values on silica. A ^{13}C NMR spectroscopic analysis of an enriched fraction from chromatographic separation of the crude reaction mixture show the key resonances expected for **123** [δ 26.5,32.6 (methyls); 81.2 (C12,C16); 101.1 (C14)].

4.1.4 Attempted synthesis of **124.**

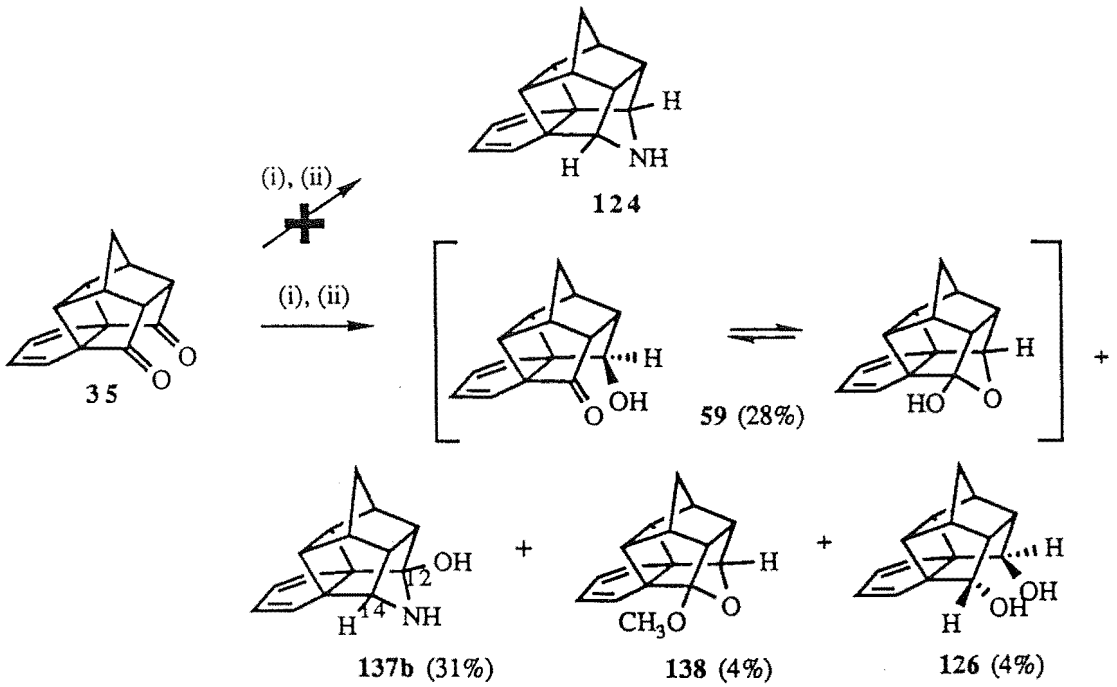
Reagents for the selective reduction of functional groups have been prepared by modifying the reducing power of complex metal hydrides.[119] An example of a particularly successful modification is that of the substituted borohydrides where the steric and electronic effects of the substituents greatly influence the reactivity of the borohydride ion. For example, sodium cyanoborohydride with its strongly electron withdrawing cyano group is a milder and more selective reducing agent than sodium borohydride.[120,121]

The reduction of aldehydes and ketones with sodium cyanoborohydride is pH dependent and the reaction proceeds readily only at *ca.* pH 3 to 4. Reaction of an aldehyde or ketone with ammonia, a primary or secondary amine at *ca.* pH 7 in the presence of the cyanoborohydride anion results in the preferential reduction of the imminium ion. Thus, a reductive amination of the carbonyl group occurs to give

primary, secondary or tertiary amines.[122,123,124] In the case of 1,4- or 1,5- ketoesters, ketoaldehydes and diketones, where 5- and 6- membered ring formation is feasible, this reaction can lead to pyrrolidines and piperidines via reductive aminocyclisation.[122,123]

Cage diketone **35** is a 1,4-diketone, and reductive aminocyclisation might be expected to lead to **124**. The reaction of **35** with sodium cyanoborohydride in the presence of ammonium bromide at a pH of 7.5 to 8 for 4 days, followed by acidification to pH 2 - 3 and further reaction for 3 days gave a complex mixture of products. Careful chromatographic separation of this product mixture on silica resulted in the isolation of four compounds, **126**, **137b**, **59** and **138** [**Scheme 4.7**]. The anticipated **124** was not formed; instead the hemiaminal **137b** was obtained in 31% yield. This product **137b** arises from the transannular cyclisation of the initially formed product, the *endo*-aminoketone **137a**.

Scheme 4.7

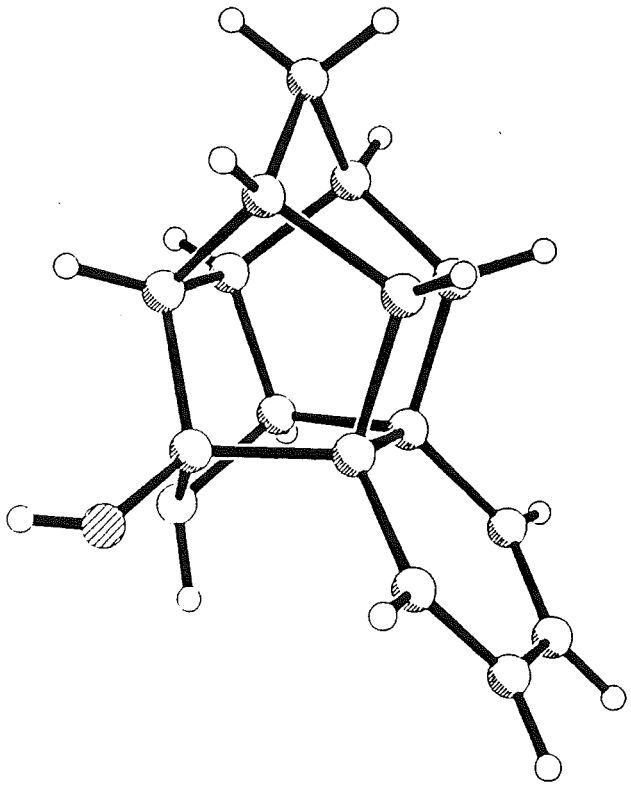


(i) NH_4Br, $NaBH_3CN$, MeOH, pH 7 - 8, 4 days, RT (ii) acidified to pH 3, 3 days, RT

The ^1H NMR and ^{13}C NMR spectra of hemiaminal **137b** are consistent with the assigned structure. In particular the methine proton at C14 resonates at 3.31 ppm (d, J = 4.5 Hz) and the OH and NH signals are observed as a broad signal between 2.4 - 3.5 ppm. The protonated C14 carbon signal is at 66.5 ppm while the quartenary C12 carbon

was not observed. The structure of hemiaminal **137b** was confirmed by an X-ray crystal structure determination. Figure. 4.2, shows a perspective view of the structure.

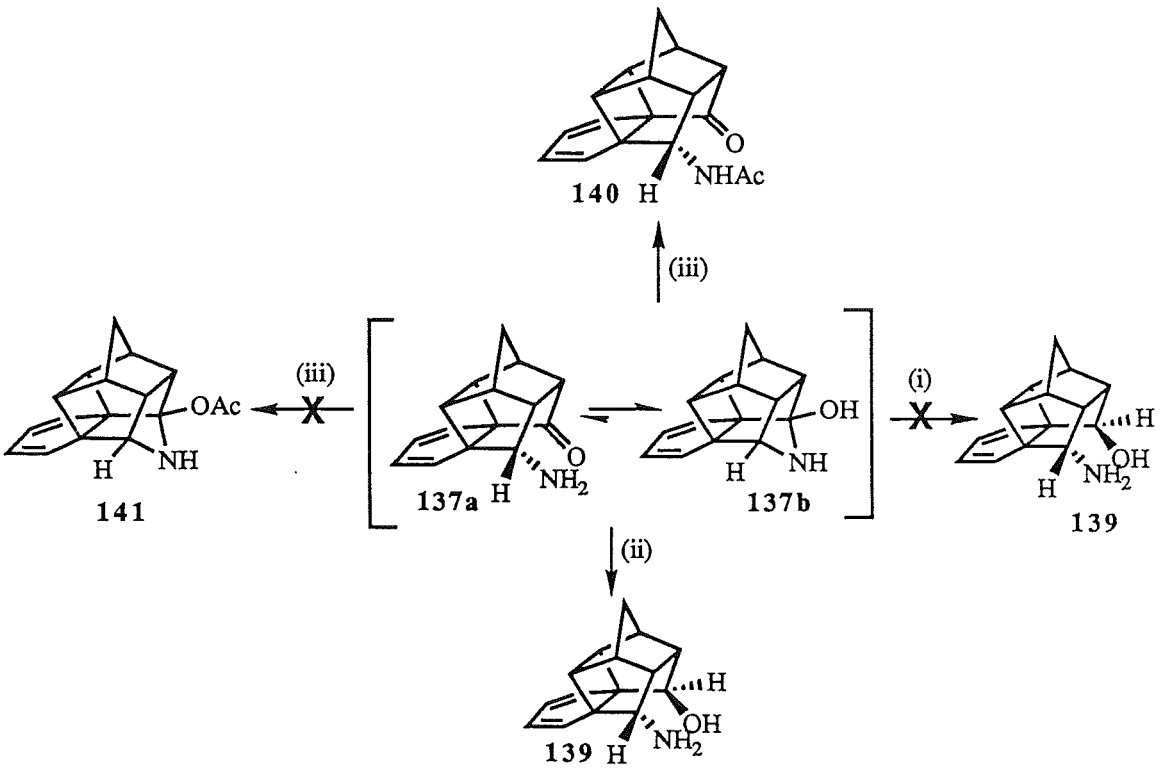
Figure 4.2. X-ray structure of **137b**



It appeared that at a lower pH, for example a pH of 2 to 3, the equilibrium of **137a** and **137b** as shown in Scheme 4.8, lies to the right and the compound exists mainly as the cyclised hemiaminal **137b**. Therefore, in this form, reduction of the ketone group by sodium cyanoborohydride cannot proceed to form **139**. This rationale was supported by the separate conversion of **137** to **139** using sodium borohydride in methanol at neutral pH.

Acetylation of hemiaminal **137b** with a mixture of acetic anhydride and pyridine gave the *endo*-amide ketone **140** resulting from acetylation of the amino group of the unbridged *endo*-aminoketone **140**. None of the corresponding O-acetylation product **141** arising from reaction with the hemiaminal **137b** was observed [**Scheme 4.8**].

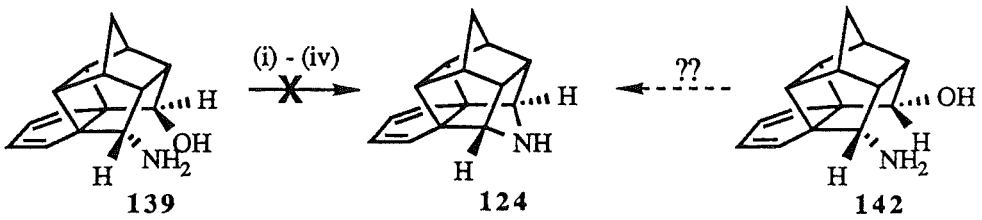
Scheme 4.8



(i) $NaBH_3CN$, methanol, pH3, 3days at RT (ii) $NaBH_4$, methanol, ca. neutral pH, RT, 12 hours.
(iii) Ac_2O, pyridine, RT, 12 hours

Various attempts to dehydrate the *endo-endo* aminoalcohol **139** with (i) p-toluenesulphonic acid heated under reflux in benzene for 43 hours ($-H_2O$), (ii) acidified methanol heated under reflux for 41 hours, (iii) PPh_3/Br_2 in acetonitrile at room temperature[125] and (iv) PPh_3 and diethyl azodicarboxylate in dichloromethane at room temperature (Mitsunobu reagent)[126] all failed to produce **124** and resulted in the recovery of **139** [**Scheme 4.9**]. This is perhaps not surprising if one considers the possible mechanisms through which **124** could be formed from the aminoalcohols **139** and **142**.

Scheme 4.9



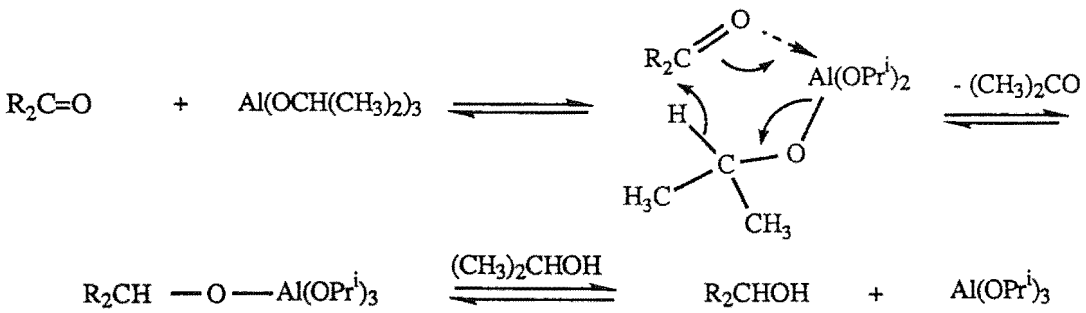
(i) p-TsOH, C_6H_6, 80°C, 43 hours (iii) PPh_3Br_2, CH_3CN, RT
(ii) H^+/methanol, reflux, 41 hours (iv) PPh_3, diethyl azodicarboxylate, CH_2Cl_2, RT

In the case of formation of **124** from **139**, an S_N2 type mechanism would not be favoured since the hydroxyl precursor to the leaving group (H_2O or Ph_3P= O) is not

positioned in an appropriate orientation for backside attack by the nitrogen nucleophile. An S_N1 type mechanism, wherein a carbocation is formed initially on the loss of the hydroxyl group, is feasible but would suffer from interference of side reactions such as rearrangement leading to aromatic product(s) as mentioned previously. Also, in the case of an acid catalysed reaction, the amino would be protonated before the hydroxyl group and the nucleophilicity of the amino group would therefore be decreased. The *endo*-amino-*exo*-hydroxyl compound **142** is geometrically disposed towards reaction through an S_N2 type mechanism and so attempts were made to prepare **142**.

Sodium borohydride reduction of **35** led largely to the formation of *endo-endo* diol **126** in a reaction that is kinetically-controlled. On the other hand, Meerwein-Ponndorf-Verley reduction of carbonyl groups[127,128] using aluminium isopropoxide and isopropanol are known to yield the thermodynamically more stable alcohol products,† since these reactions are reversible. The Meerwein-Ponndorf-Verley reactions are usually considered to involve a cyclic "transition state" structure [**Scheme 4.10**].[129,130] An equilibrium is reached between the ketone and isopropoxide and the alcohol and acetone. Continuous distillation of the most volatile component, acetone, displaces the equilibrium in favour of the alcohol. One equivalent of aluminium isopropoxide is sufficient since it is regenerated by reaction of the aluminium derivative of the product with isopropanol. However, an excess is usually employed to increase the rate of the reaction and to reduce side reactions.

Scheme 4.10

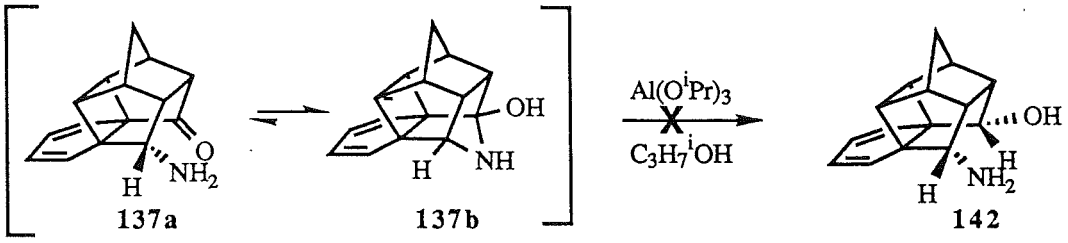


Reaction of **137** with aluminium isopropoxide in isopropanol did not lead to **142** and **137b** was recovered [**Scheme 4.11**]. There are two possible reasons for this

† Molecular mechanic modelling (BAKMDL 1991) of the *endo*-hydroxy ketone **59a** and *exo*-hydroxy ketone **143** showed that the *exo*-hydroxy ketone **143** is the more stable epimer by *ca.* 3.5kJmol^{-1} and the predicted Boltzmann distribution of **59a**:**143** at 81°C is 23%:77%.

failure; firstly the reaction may start from an unfavourable equilibrium position of **137a** and **137b**. The reduction can only proceed from the unbridged compound **137a**. Secondly, the rigidity of the cage structure is such that the *endo*-amino group will provide steric hindrance and the formation of a cyclic "transition state" structure involving the carbonyl group may not be geometrically possible and therefore would not be favoured.

Scheme 4.11



137a **137b** **142**

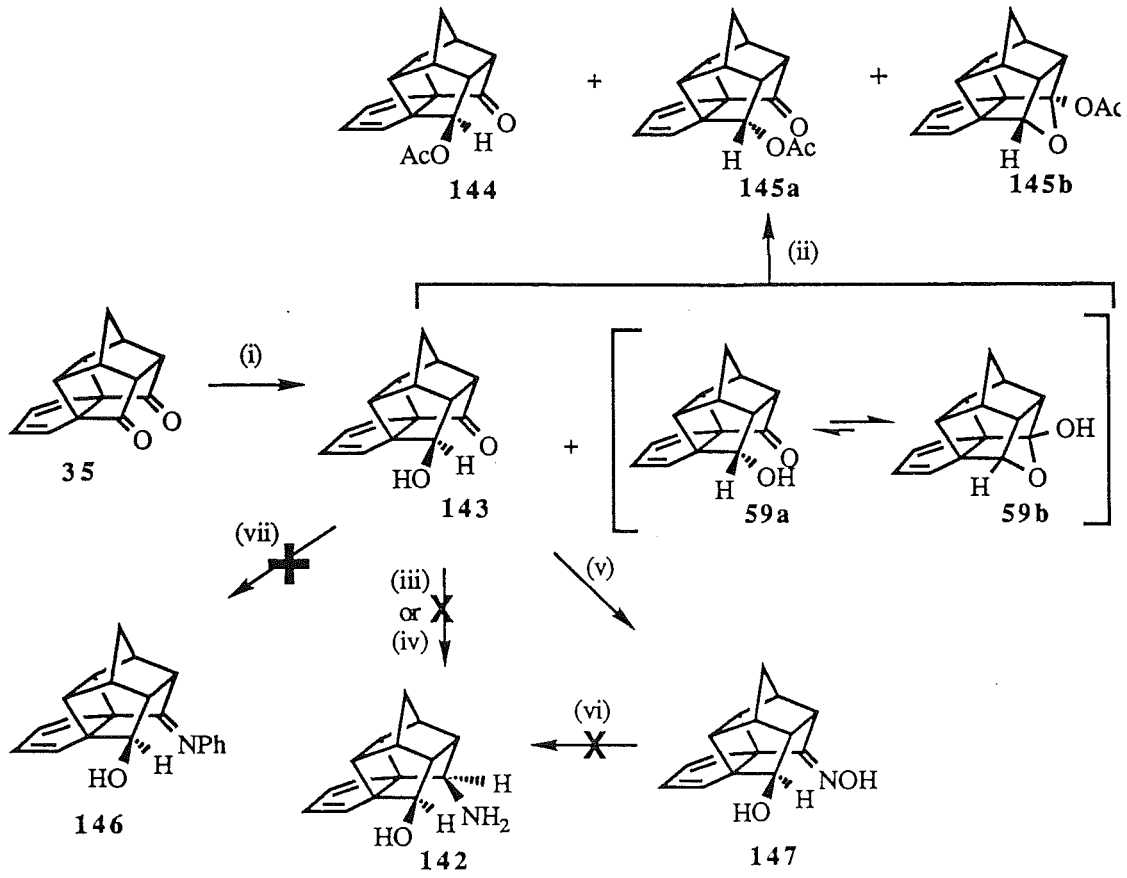
These explanations for the failure to effect reaction, were substantiated by the reaction of the cage diketone **35** with aluminium isopropoxide in isopropanol, wherein an equilibrium mixture of the *exo*-hydroxyketone **143** and *endo*-hydroxyketone **59** was produced. Futhermore, the *endo*-hydroxyketone can undergoes transannular cyclisation and hence exists as an equilibrium mixture of **59a** and **59b**. Acetylation of this product mixture with acetic anhydride/pyridine gave the corresponding acetates **144**, **145a** and **145b** [**Scheme 4.12**].

It is noteworthy that unlike sodium borohydride reduction of **35**, a Meerwein-Ponndorf-Verley reduction of the diketone resulted largely in the reduction of one of the two carbonyl groups. This is possibly due to the steric demand of a cyclic "transition state" structure. The ^{1}H NMR spectrum of the crude reaction mixture showed only a trace amount of the *endo-exo* diol. Careful chromatographic separation of this mixture of alcohol products gave a pure sample of the *exo*-hydroxy ketone **143** (31%). However, surprisingly, reductive amination of **143** with ammonium bromide/sodium cyanoborohydride/methanol at a pH of 7 to 8 did not afford the *endo*-amino-*exo*-hydroxy compound **142**. A modified reductive amination procedure involving titanium isopropoxide, which has been reported to catalyse imminium formation[131] was tried but in our hands did not effect this conversion [**Scheme 4.12**].

An attempt was also made to prepare the Schiff base **146** which could subsequently be reduced to an amine. Reaction of *exo*-hydroxyketone **143** with aniline in benzene

with azeotropic removal of water/benzene resulted in an intractable mixture and, from infrared and NMR spectroscopic analyses, it appeared the Schiff base **146** was not formed [**Scheme 4.12**].

Scheme 4.12

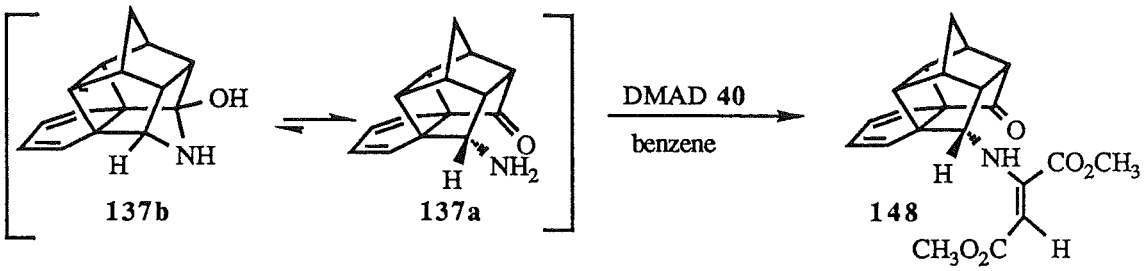


(i) $Al(O^iPr)_3$ (ii) Ac_2O,pyridine (iii) NH_4Br, $NaBH_3CN$, methanol (iv) NH_4Br, $NaBH_3CN$, methanol, catalyst ($Ti(O^iPr)_4$) (v) $H_2NOH.HCl$, K_2CO_3, ethanol (vi) $LiAlH_4$, THF (vii) aniline, benzene (- H_2O)

Exo-hydroxyketone **143** was reacted with hydroxylamine in ethanol to produce the mono-oxime **147**. However, further reduction of this oxime with lithium aluminium hydride in tetrahydrofuran failed to give **142** [**Scheme 4.12**].

Reaction of hemiaminal **137b** with the dienophile DMAD **40** resulted in a "Michael-type" addition involving the amino group of **137a** and the acetylenic moiety of DMAD to give the adduct **148**. The expected Diels-Alder reaction of the diene moiety of **137b** with the dienophile did not occur [**Scheme 4.13**]. Reaction of the hemiaminal **137b** with MA **38** and PTAD **41** resulted in similar side reactions leading to mixtures of products, ^1H NMR of which showed the presence of the cyclohexadienyl moiety.

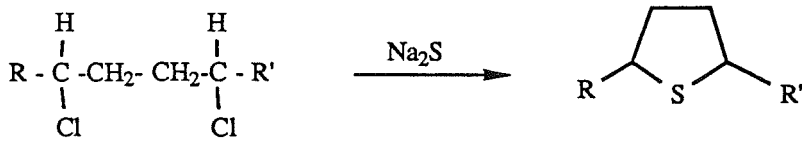
Scheme 4.13



4.1.5 Attempted synthesis of cyclic sulfide **125.**

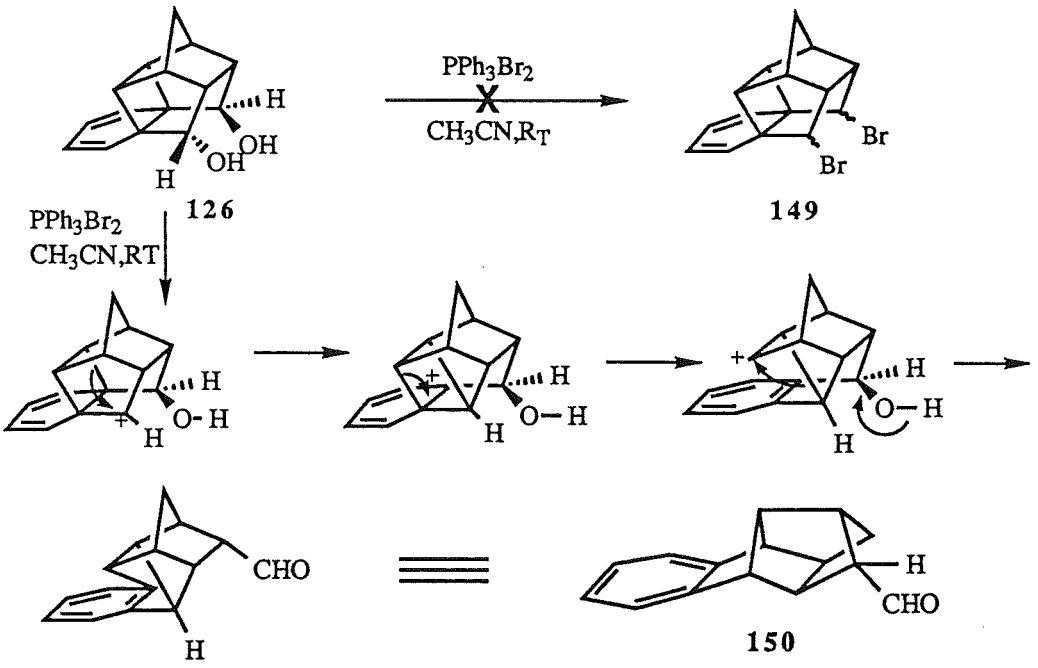
1,4-Dihalides are known to react with sulphide anion to form a cyclic sulphide [**Scheme 4.14**].[132]

Scheme 4.14



In order to apply this methodology to the preparation of the cyclic sulfide **125**, a supply of the dihalide precursor **149** is required. Reaction of *endo-endo* diol **126** with triphenylphosphine dibromide in acetonitrile did not produce the dihalide **149.** Instead, the *endo-endo* diol rearranges to an aromatic aldehyde which is tentatively assigned as **150.** A proposed mechanism for its formation is shown in Scheme 4.15.

Scheme 4.15



4.2 Diels-Alder reactions of ether 121, cyclic acetal 122 and amide 140.

Addition reactions of the cage ether **121**, cyclic acetal **122** and amide **140** were performed with representative dienophiles selected from the alkene, alkyne and azo classes. The product ratios were determined by 300 MHz ^{1}H NMR spectral analysis of crude reaction mixtures. The stereochemistries of the adducts were determined mainly by nuclear Overhauser effect difference spectroscopy (NOED) as described previously. The results are summarised in Table 4.1.

Table 4.1. Product Ratios[a] for the Diels-Alder reactions[b] of ether **121**, acetal **122**, amide **140**, **35**[58], **36a** and **36b**.[62]

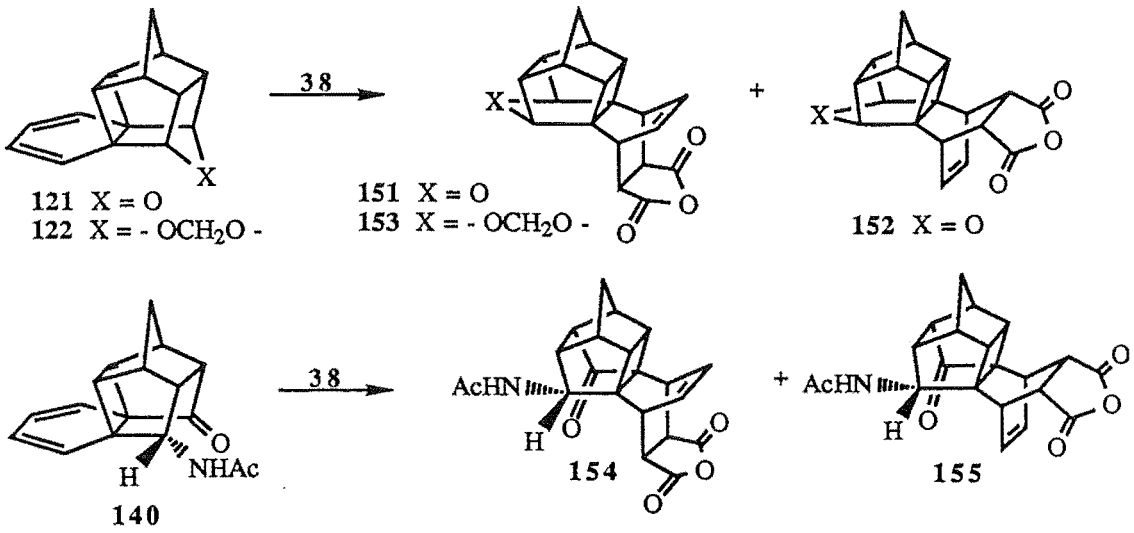
Dienophiles	% reaction at the "bottom face" of the dienes					
	121	**122**	**140**	**35**	**36a**	**36b**
MA (**38**)	96	100	86	100	100	85
DMAD (**40**)	8	10	50	55	25	10
MP (**73**)	8	20	-	100	66	-[c]
PTAD (**41**)	5	3	98	64	78	93
NB (**74**)	6	0	-	-	-	-

[a]Product ratios (± 2%) from 300 MHz ^{1}H NMR analysis of crude reaction mixtures.
[b]All reactions were conducted in benzene at 80°C except for reactions involving PTAD **41** which were conducted in dichloromethane at 0-5°C.
[c]No reaction after prolonged reflux.

4.2.1 Reactions with maleic anhydride 38.

Reaction of ether **121** with maleic anhydride (MA) **38** gave "bottom face" to "top face" adducts **151** and **152** in a ratio of 96%:4%. The cyclic acetal **122** reacted with MA **38** to give the "bottom face" adduct **153** in 100% stereochemical yield. This facial selectivity is similar to that observed in the reaction of diketone **35** with MA **38** where exclusive formation of the corresponding "bottom face" adduct was observed.[58] Amide **140** reacted with MA **38** to give 86% of the "bottom face" adduct **154**, which is similar to the reaction of dimethylidene **36b** with MA **38** where 85% of the "bottom face" adduct was formed [**Scheme 4.16**].

Scheme 4.16

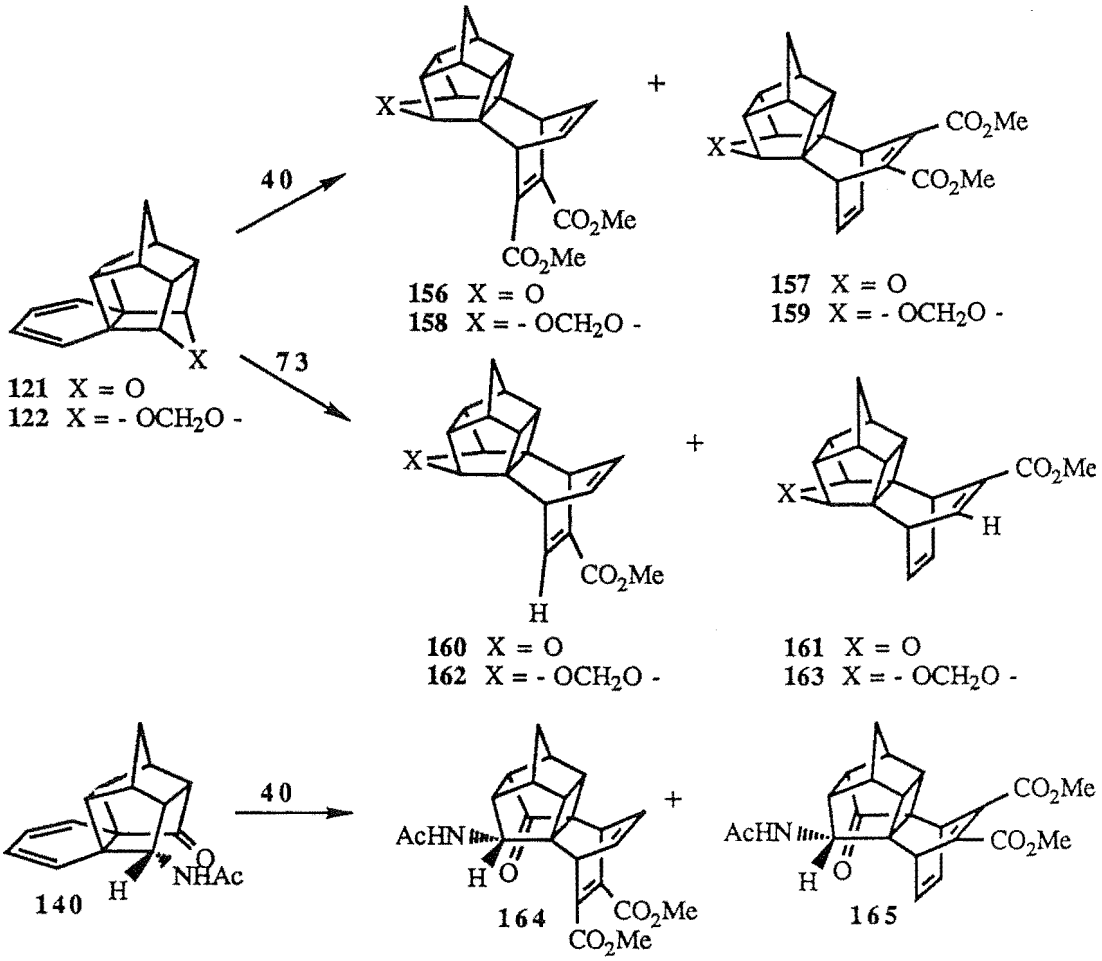


The alkene dienophile MA **38** shows a strong preference for the "bottom face" of the cage ether **121** and cyclic acetal **122** and these reactions seemed to be under steric control since the "bottom face" of these dienes is relatively unhindered. The situation for the amide **140** changes with the introduction of a more bulky acetate group on the nitrogen, hence the "bottom face" is now more hindered to MA **38** which possesses hydrogens syn to the C=C. This, in turn, allows for competitive reaction from the "top face" which occurs significantly and 14% of the "top face" adduct **155** is obtained [**Scheme 4.16**].

4.2.2 Reactions with alkyne dienophiles

Reaction of cage ether **121** with the electron deficient dienophile dimethylacetylene dicarboxylate (DMAD) **40** or methyl propiolate (MP) **73** resulted in a predominant preference for the "top face" of the diene leading to the formation of 92% of the "top face" adducts **157** or **161** and 8% of the "bottom face" adducts **156** or **160** [**Scheme 4.17**]. In contrast, the reaction of **35** with DMAD **40** gave 55% of the "bottom face" adduct.[58] Thus, replacing the dicarbonyl subtituents with a centrally placed oxygen bridging group has a remarkable influence on the observed π-facial selectivities. This suggests that the strategically placed oxygen with its attendant lone pair electrons is responsible, possibly by destablising the "transition state" structure of the "bottom face" adducts through interactions of the filled orbitals of DMAD which are orthogonal to the forming σ-bonds in the reaction.

Scheme 4.17



The cyclic acetal **122** also reacted with DMAD **40** or MP **73** to give largely the "top face" adducts **159** or **163** in 90% and 80% stereochemical yields [**Scheme 4.17**]. This result is again attributed to the presence of the lone pair electrons on the oxygens of the acetal **122**.

Reaction of the amide **140** with DMAD **40** was not facially selective resulting in the formation of a 50%:50% mixture of the "bottom face" and "top face" adducts **164** and **165** [**Scheme 4.17**]. This is similar to the reaction of diketone **35** with DMAD where "bottom face" and "top face" adducts were formed in 55% and 45% respectively.

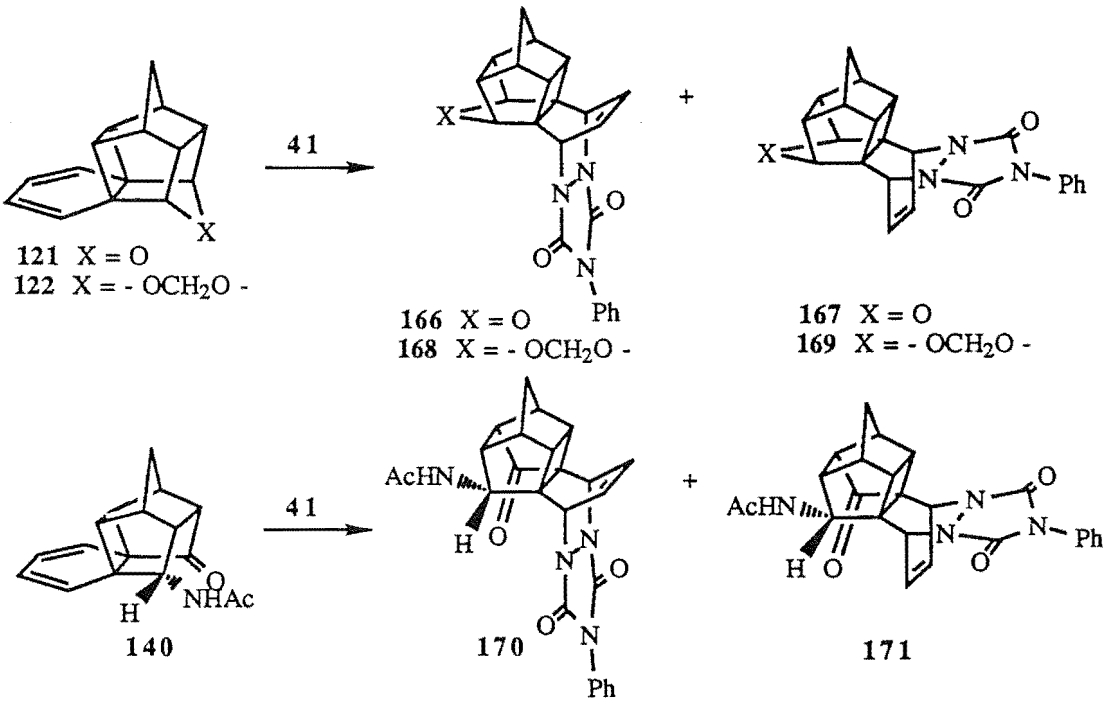
4.1.3 Reactions with N-phenyltriazoline dione (PTAD) **41**.

Cage ether **121**, cyclic acetal **122** or amide **140** reacted with PTAD **41** to give the corresponding adducts **166 -171[Scheme 4.18]**.

Cage ether **121** reacted with PTAD **41** to give 5% of the "bottom face" adduct **166** and 95% "top face" adduct **167** compared with diketone **35** wherein 64% and 36% of the

"bottom face" and "top face" adducts were produced. This predominant preference for the "top face" of the diene is also seen in the reaction with the cyclic acetal **122** wherein 97% of the "top face" adduct **169** was observed. These results are the only cases where such a clear preference for the "top face" of a cage diene is shown in a reaction with PTAD **41**. Clearly, the strategically placed "lone pair" electrons are involved in this π-facial selectivity, possibly by destablising the "transition state" structure of the "bottom face" adduct through electron repulsion between "lone pair" electrons on the oxygen bridge and the azo nitrogen of PTAD **41**.

Scheme 4.18



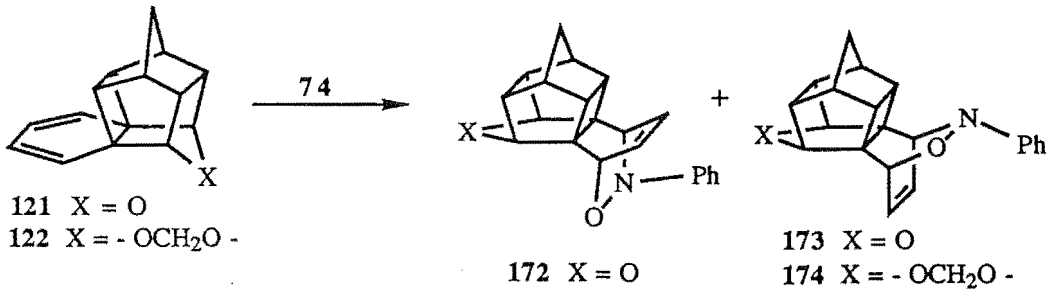
Amide **140** reacted with PTAD **41** to give predominantly (98%) the "bottom face" adduct **170**. This selectivity is similar to that of the dialkane **103** wherein exclusive formation of the corresponding "bottom face" adduct was observed [**Scheme 4.18**].

4.1.4 Reactions with nitrosobenzene **74**.

Reaction of cage ether **121** or cyclic acetal **122** with nitrosobenzene **74** gave preferentially the "top face" adducts **173** or **174** in 94% and 100% stereochemical yields [**Scheme 4.19**]. The reaction of cage ether **121** with nitrosobenzene **74** is reversible. After 9 hours of reflux in benzene, the amount of unreacted ether **121** in the reaction mixture was greater than the previous ^{1}H NMR analysis of the reaction mixture after a

reaction period of 7 hours. However, the ratios of the "top face" and "bottom face" adducts **173** and **172** were similar implying that the reaction had not proceeded to equilibrium. Therefore the reported result is for the kinetic controlled reaction.

Scheme 4.19



4.3 Molecular mechanics calculations

Force-field calculations (MMX or MM2) were performed on the products and "transition state" structures of the reactions of cage ether **121** and cyclic acetal **122** with selected dienophiles [**Tables 4.2** and **4.3**].

Table 4.2 shows that the predicted selectivity for the "bottom face" of ether **121** or cyclic acetal **122** based on product stability differs markedly from the experimentally observed selectivities, again indicating product stability is not the determining factor involved in diastereofacial selection in these cases.

Table 4.2. Calculated (MMX) energy differences ($\Delta E_{(bottom - top)}$, kJ mol^{-1}) between adducts resulting from "bottom face" and "top face" reaction ($\Delta E_{(B-T)}$) and calculated percentage "bottom face" reaction at 80°C (% calcd) of ether **121** and acetal **122** with selected dienophiles compared with experimental result (exp).

Dienophiles	Ether **121**			Acetal **122**		
	$\Delta E_{(B-T)}$ kJ mol^{-1}	% calcd	% exp	$\Delta E_{(B-T)}$ kJ mol^{-1}	% calcd	% exp
MA (**38**)	- 6.2	89	96	-3.6	77	100
DMAD (**40**)[a]	- 2.3	68	8	-6.5	90	10
PTAD (**41**)[b]	-2.4	73	5	-1.7	67	3

[a]Calculated using BAKMDL (MM2) energy difference between the average energy of significant conformers at 80°C.
[b]Calculated at 0°C.

On the other hand, Table 4.3 indicate that the predicted selectivity for the "bottom face" of ether **121** or acetal **122** with MA **38** based on the MMX "transition state" structures agree very well with the experiment results i.e. 93% versus 96% or 95 versus 100%. These results are consistent with the trend for the calculated MMX Diels-Alder "transition state" structures of reactions between cage dienes and alkene dienophiles, where good agreements between predicted adduct ratios and experimental results are obtained. Thus, steric factors are considered to be important in determining π-facial selectivity in these Diels-Alder reactions of dienes **121** and **122** with MA **38**. The MM "transition state" (fixed model) calculation on the reaction of cage ether **121** or cyclic acetal **122** with DMAD **40** predicted the formation of the "bottom face" adduct at 78% or 100% compared with the experimental result of 8% or 10% respectively. Since molecular mechanics calculations do not include electronic effects, the disparity in the case of reactions with DMAD indicate that such effects are likely to be dominant.

Table 4.3. Energy differences between transition states ($\Delta E_{(bottom\text{-}top)}$, kJ mol^{-1}) calculated using MMX transition state parameters and predicted percentage reaction at the "bottom face" of the Diels-Alder reactions.

Dienophiles	Ether **121**			Acetal **122**		
	$\Delta E_{(B\text{-}T)}$ kJ mol^{-1}	% calcd	% exp	$\Delta E_{(B\text{-}T)}$ kJ mol^{-1}	% calcd	% exp
MA (**38**)	- 7.7	93	96	-8.6	95	100
DMAD (**40**)[a]	- 3.7	78	8	-28.3	100	10

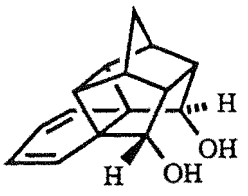
[a]Difference is between average Boltzmann energy of significant conformers at 80°C, calculated using a fixed model based on AM1 transition state calculations for acetylene and cyclohexadiene (ref 62).

Chapter 5

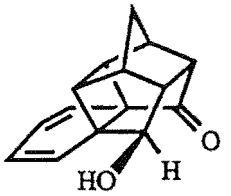
Diels-Alder reactions of an hydroxyketone and its acetate analogue

Diastereofacial selection in Diels-Alder reactions of the *endo-endo* diol **126** have been studied and the exclusive selectivity of the alkene, acetylenic and azo type dienophiles for the "bottom face" of this diene is remarkable.[93] In the previous study, molecular mechanic calculations on both the product stabilities and steric energies of "transition state" structures successfully predicted this selectivity. Since there is no experimental evidence for reversibility in these reactions with the exception of reactions with nitrosobenzene, it seems that the thermodynamically most stable product is coincidentally also the kinetic product. The observed selectivity was ascribed to steric effects which are the dominant factors governing this facial selection. Hydrogen bonding interactions between the hydroxyl substituents and incoming dienophiles[95] were considered not relevant as there was no evidence of such interactions in the modelling studies and the observation that intramolecular hydrogen bonding was highly favoured in the *endo-endo* diol **126**.

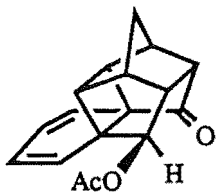
However, as described in Chapter 4, the bridged ether **121** and bridged acetal **122**, which have similar steric demands and similar dispositions of the oxygen atoms to the *endo-endo* diol **126**, undergo reactions with acetylenic and azo dienophiles preferentially from the "top face". Thus perhaps hydrogen bonding is in fact important in directing dienophiles to the bottom face of the diol.



126



143



144

35

In order to investigate further into facial selectivity in such cage diene substrates where hydrogen bonding between the diene and incoming dienophiles is possible, the Diels-Alder addition reactions between *exo*-hydroxyketone **143** and representative

dienophiles from the alkene, acetylenes and azo classes were performed. The *exo*-hydroxyketone **143** is of interest, firstly, because it is the closest "intermediate" case between the *endo-endo* diol **126** and the diketone **35**. The *endo*-hydroxyketone **59a** would not be suitable for this study as the *endo*-hydroxyl group undergoes a cyclisation reaction with the transannular carbonyl moiety to the hemiacetal **59b**. Secondly, in **143**, intramolecular hydrogen bonding interactions between the *exo*-hydroxy group and the transannular ketone moiety is geometrically not possible. Therefore, the hydrogen of the hydroxyl group would be available for intermolecular hydrogen bonding interactions if such interactions are possible in these Diels-Alder reactions. Furthermore, the reactions of the acetylated derivative **144** of the *exo*-hydroxyketone **143**, in which the hydroxyl group is protected, would also be of interest as the possibility of hydrogen bonding interaction is removed.

5.1 Diels-Alder reactions of the *exo*-hydroxy- and *exo*-acetoxyketones.

The reactions of *exo*-hydroxyketone **143** and *exo*-acetoxyketone **144** with the representative dienophiles, maleic anhydride **38**, dimethylacetylene dicarboxylate **40** and N-phenyltriazoline dione **41** from the alkene, acetylene and azo classes proceeded smoothly at approximately the same rates as that of the diol **126** and diketone **35**. The product ratios are summarised in Table 5.1. Product ratios were determined by 300 MHz NMR spectral analysis of crude reaction mixtures. The stereochemistries of the adducts were determined by nuclear Overhauser difference spectroscopy (NOED), by the mutual enhancement between the olefinic protons and the cyclobutane ring protons as previously described.

Table 5.1. Product Ratios[a] for the Diels-Alder reactions[b] of **143**, **144**, **126**[93] and **35**.[58]

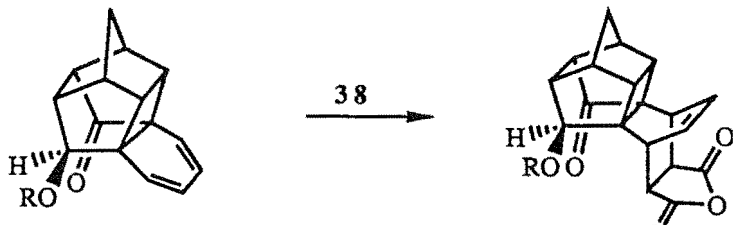
Dienophiles	% reaction at the "bottom face" of the dienes			
	143	**144**	**126**	**35**
MA (**38**)	100	100	100	100
DMAD (**40**)	100	100	100	55
PTAD (**41**)	100	100	100	64

[a]Product ratios (± 2%) from 300 MHz ^{1}H NMR analysis of crude reaction mixtures. [b]All reactions were conducted in benzene at 80°C except for those involving PTAD **41** at 0 - 5°C in CH_2Cl_2.

5.1.1 With maleic anhydride (MA) **38.**

The alkene dienophile, maleic anhydride **38** reacted with the *exo*-hydroxyketone **143** or *exo*-acetoxyketone **144** to give exclusively the "bottom face" adduct **175** or **176** [**Scheme 5.1**].

Scheme 5.1



143 R = H
144 R = Ac

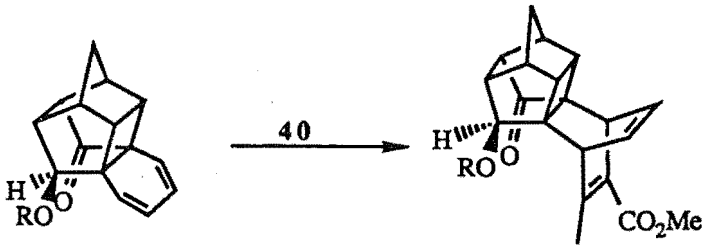
175 R = H
176 R = Ac

This is similar to the selectivity reported for the *endo-endo* diol **126** and the cage diketone **35** wherein 100% of the corresponding "bottom face" adducts were formed.

5.1.2 With dimethylacetylene dicarboxylate (DMAD) **40.**

Reaction of the diene **143** or **144** with the acetylenic dienophile, dimethylacetylene dicarboxylate **40** gave only a single adduct, which is the "bottom face" adduct **177** or **178** [**Scheme 5.2**]. It is noteworthy that this high facial selectivity is similar to that observed for the *endo-endo* diol **126** and unlike the reaction of diketone 35 wherein 45% of the "top face" adduct was formed. The presence of a ketone moiety in the diene did not appear to be effective in forcing the dienophile away from the "bottom face". However, hydrogen bonding as a dominant factor in this facial selection can be ruled out since the reaction of dimethylacetylene dicarboxylate with the acetylated analogue **144** also showed the same exclusive selectivity.

Scheme 5.2



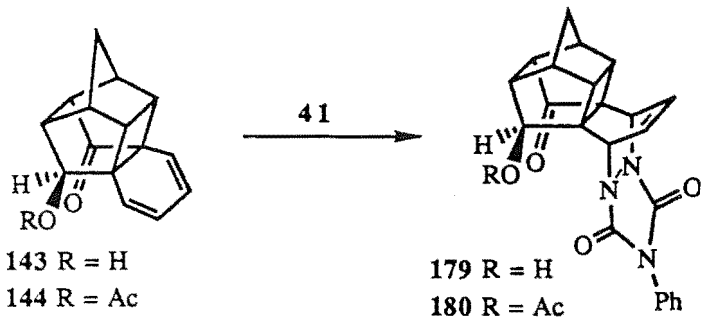
143 R = H
144 R = Ac

177 R = H
178 R = Ac

5.1.3 With N-phenyltriazoline dione (PTAD) **41.**

Reaction of *exo*-hydroxyketone **143** or *exo*-acetoxyketone **144** with N-phenyl-triazoline dione **41** gave exclusively the "bottom face" adduct **179** or **180** which is comparable to the reaction of this dienophile with the *endo-endo* diol **126** but differs from cage diketone **35** wherein 36% of the "top face" adduct was formed [**Scheme 5.3**]. The exclusive formation of the "bottom face" adduct in the reaction of *exo*-acetoxyketone **144** with PTAD **41** further proves that there is no involvement of hydrogen bonding between **143** and PTAD.

Scheme 5.3



143 R = H
144 R = Ac

179 R = H
180 R = Ac

5.2 Molecular mechanics calculations

Force-field calculations (MM2) were performed on the products and "transition state" structures of the reactions of *exo*-hydroxyketone **143** with MA **38**, DMAD **40** and PTAD **41** [**Tables 5.2** and **5.3**]. The MM2 force-field was used to allow for conformational searching of the hydroxyl bond in these structures and, in the case of the DMAD adduct , the carboxylate groups.

Table 5.2 shows that the predicted percentages of the diastereomeric adducts based on product stabilities differs from the experimentally observed selectivities. This again indicates that product stabilities is not a dominant factor in π-facial selectivity.

Table 5.3 reveals that calculations which are based on a "steric only" model of the diastereomeric "transition state" structures of the Diels-Alder reactions of **143** with MA **38** and DMAD **40** predicted the experimental results very well. This indicates that for the *exo*-hydroxyketone **143** steric interactions at the "transition state" are the dominant factor governing facial selection. This result is consistent with that reported for the Diels-Alder reactions of the *endo-endo*-diol **126.**

Table 5.2. Calculated (MM2) energy differences ($\Delta E_{(bottom - top)}$, kJ mol^{-1}) between adducts resulting from "bottom face" and "top face" reaction ($\Delta E_{(B-T)}$) and calculated percentage "bottom face" reaction at 80°C (% calcd) of *exo*-hydroxyketone **143** with selected dienophiles compared with experimental result (exp).

Dienophile	$\Delta E_{(B-T)}$ kJ mol^{-1}	*exo*-hydroxyketone **143** % calcd	% exp
MA (**38**)	- 3.4	76	100
DMAD (**40**)	- 0.44	46	100
PTAD (**41**)[a]	4.1	16	100

[a]Calculated at 0°C.

Table 5.3. Energy differences between transition states ($\Delta E_{(bottom-top)}$, kJ mol^{-1}) calculated using MMX transition state parameters and predicted percentage reaction at the "bottom face" of the Diels-Alder reactions of **143** with selected dienophiles.

Dienophile	$\Delta E_{(B-T)}$ kJ mol^{-1}	*exo*-hydroxyketone **143** % calcd	% exp
MA (**38**)[a]	- 11.7	99	100
DMAD (**40**)[a,b]	- 22.9	100	100

[a]Difference is between average Boltzmann energy of significant conformers at 80°C.
[b]Calculated using a fixed model based on AM1 transition state calculations for acetylene and cyclohexadiene (ref.62).

Chapter 6

Conclusion

6.1 Chemistry of the diene-fused cage compounds

The syntheses of cage substrates for subsequent π-facial selectivity studies showed clearly that there are substantial differences between functional group interconversions in the pentacycloundecane series (PCUD) and the hexacyclopentadecadiene series. For the PCUD dione **60**, the following standard functional group interconversion reactions all proceeded smoothly in average to good yields: (i) Wolff-Kishner reduction to form the dialkane, (ii) acid-catalysed dehydration of diols, (iii) condensation reactions with nitrogen nucleophiles and (iv) nucleophilic substitution of diols by halides. The corresponding reactions with the diene-fused cage diketone **35**, or a suitable derivative of **35**, proceeded with great difficulty resulting in either low yields or complex mixtures of unidentified products. The rigid cage structure of both the PCUD dione **60** and the diene-fused cage diketone **35** would imply that the geometry at the substituent C3 and C10 positions should be very similar. This expectation has been proved by the modelling studies of both compounds, X-ray determined structural studies of analogues of **60** and **35**, and also the general observation of the similar ease of transannular cyclisation reactions involving the atom centers 3 and 10. The different chemistries of these diones is attributed to the presence of the cyclohexadienyl moiety in **35** which promotes rearrangement reactions leading to reformation of the aromatic ring once substantial positive charge is generated at one of the C3 or C10 centers. The ease of these rearrangement reactions is shown by the isolation of (i) the aromatic product tentatively assigned as **150** from the reaction of diene-fused cage diol **126** with triphenylphosphine dibromide and (ii) the pentacyclic pyridazine derivative **134** from the reaction of tosylhydrazone **106** with an alcohol.

6.2 π-Facial selectivity

The factors determining π-facial selectivity in these substrates depend on both the substituents on the diene and the dienophile employed. Some general findings from this study are:

(i) The observed facial selectivity is independent of product stabilities. This was seen in the inability of molecular mechanics calculations of the "steric energies" of the diastereomeric adducts to correctly predict the experimental isomer product distributions and is consistent with the experimentally observed non-reversibility of the reactions.

(ii) Diels-Alder reactions of alkene dienophiles with the diene-fused cage compounds showed either a high or exclusive preference for the "bottom face" of the diene. The major factor determining this facial selection appears to be steric in nature. The alkene dienophiles used in this study, all possess cis hydrogens on the C=C bond and reaction at the "bottom face" is favoured by the formation of a "transition state" structure of lower "steric energy". Presumably, reaction from the "top face" is destabilised by the non-bonded interactions between the cyclobutane ring hydrogens and the cis hydrogens of the dienophiles in the "transition state" structure.

(iii) Reactions of acetylenic dienophiles dimethylacetylene dicarboxylate (DMAD) **40** and methyl propiolate (MP) **73** with dienes such as the cage ether **121** and cyclic acetal **122** gave predominantly "top face" adducts. This is attributed to the repulsive interactions of the suitably orientated lone pair electrons in **121** and **122** with the filled orthogonal orbitals of the acetylenic dienophiles. The orientation of the lone pair orbitals are important as shown in the reaction of *exo*-hydroxyketone **143**. This diene possess lone pair electrons on the ketone moiety and the *exo*-hydroxyl group at C3 and C10, yet exclusive "bottom face" selectivity is observed in the reaction with DMAD **40** and N-phenyltriazoline dione (PTAD) **41**.

(iv) The reactions of the azo dienophile PTAD **41** with cage dienes such as cage ether **121** and cyclic acetal **122** showed the same trend in the high preference for the "top face" of these dienes. This again points to the repulsive interactions between the lone pair

electrons on nitrogen of the azo dienophile with the lone pairs on the oxygen(s) of **121** and **122** and reaction at the "top face" becomes more favourable.

(v) The importance of stereoelectronic interactions of these remote substituents at atom centers 3 and 10 in such diene-fused cage compounds is clearly seen by comparison with the reactions of the dialkane **103** with maleic anhydride **38**, DMAD **40** and PTAD **41**. These reactions show exclusive formation of the "bottom face" adducts. Therefore, in the absence of unfavourable electronic interactions at the "bottom face", addition at this face is generally preferred.

(vi) There is no evidence for hydrogen bonding interactions as a determining factor in facial selection in dienes with hydroxyl groups which are capable of intermolecular hydrogen bonding interactions with heteroatoms such as oxygen or nitrogen on the dienophiles. This is demonstrated by the crystal structure of the dioxime-PTAD adduct **119** which showed the dioxime moieties are positioned in a trans manner which would exclude such hydrogen bonding interactions at the "transition state". Furthermore, since the dienophiles DMAD **40** and PTAD **41** also attack exclusively from the "bottom face" of the hydroxy-protected diene, *exo*-acetoxyketone **144**, the exclusive preference for the "bottom face" of *exo*-hydroxyketone **143** seen in these reactions is unrelated to hydrogen bonding interactions.

EXPERIMENTAL

General

NMR spectra were recorded on a Varian XL-300 spectrometer equipped with a 5-mm probe operating at 299.930 and 75.426 MHz for ^{1}H and ^{13}C respectively. Chemical shifts are listed in p.p.m. relative to tetramethylsilane. Difference NOE spectra were obtained in an arrayed experiment with the decoupler offset 10,000 Hz and then cycled with low power over the multiplet peaks of the desired proton for irradiation, a procedure based on that of Kinns and Sanders.[90] Heteronuclear proton-carbon correlated spectra were recorded using a sequence that ensures full ^{1}H-^{1}H decoupling.[91] For several compounds the aromatic carbon signals were coincident and some non-protonated carbon signals were not observed due to limited sample availability.

Infrared spectra were recorded on Unicam SP3-300 or Perkin Elmer 1600 Series FT-IR spectrometers as KBr discs unless otherwise specified. Mass spectra were recorded on an AEI MS902 or Kratos MS 80 RFA spectrometers. Radial chromatography was performed on a Chromatotron (Harrison and Harrison) using Merck type 60P.F_{254} silica gel. Melting points were determined using an electrothermal melting point apparatus and are uncorrected. Microanalyses were performed by the Chemistry Department, University of Otago, Dunedin. In a few cases water or other solvent of crystallisation was incorporated into the crystal lattice and repeated recrystallisation yielded the same microanalytical results. All dienophiles were obtained commercially.

The general procedure for the photolyses of Diels-Alder adducts was as follows: a solution of an adduct in a quartz reaction vessel was irradiated with either a low-pressure 450W Hg lamp (Hanovia) (Pyrex filter) or in a Rayonet reactor with the specified wavelength lamps. In the case of the use of the Hg lamp, the quartz vessel was submerged in an ice-water bath whilst photolyses using the Rayonet reactor were performed without external cooling of the reaction vessel. The progress of the photolyses was monitored by ^{1}H NMR spectroscopy. All photolyses were carried out under a nitrogen atmosphere.

The general procedure for the addition reactions of the dienophiles to the cage dienes was as follows: the diene (ca. 0.50 - 1.00 mmole) was dissolved in benzene. To this a slight excess of the dienophile was added and the reaction was heated under reflux. The progress of the reaction was followed by either t.l.c. (silica gel with a 3:2 mixture of ether and petroleum ether as elutant) or ^{1}H NMR. When either no starting material could be detected or sufficient product(s) were obtained (2 hours to 173 days), the solvent was removed and ^{1}H and ^{13}C NMR spectra of the crude product were recorded and the product ratios were determined. The crude reaction mixtures were then separated either by recrystallisation, by radial chromatography on silica gel or by hplc.

The stereochemistries of the adducts were determined largely by nuclear Overhauser effect difference (NOED) spectroscopy[90] and in a few instances by X-ray crystallography. NOED proved particularly useful for distinguishing between "bottom face" adducts **42** and "top face" adducts **43**. A typical example is shown in Figure 4.3. The normal 300 MHz ^{1}H NMR spectrum of the ether-maleic anhydride adduct **151** is shown in Figure 4.3a along with the proton assignments which were determined on the basis of NOED experiments and comparisons of chemical shifts values of known adducts. The NOED spectrum resulting from irradiation of the olefinic protons H_x is shown in Figure 4.3b. This spectrum shows significant enhancement of the signals due to the spatially proximate protons, H_p and H_e. Similarly, irradiation of H_e (Figure 4.3c) results in enhancements of the signals for the proximate protons H_b, H_d, H_p and H_x. The mutual enhancements observed between H_e and H_x are clearly only consistent with the structure resulting from dienophile attack on the "bottom face" of the cage ether.

With the ^{1}H NMR spectrum assigned, the ^{13}C NMR spectrum was assigned by means of heteronuclear two-dimensional correlation spectroscopy.[91] This is exemplied in Figure 4.4 for the ether-maleic anhydride adduct **151** in which the ^{13}C NMR spectrum, on the horizontal axis is assigned from the cross correlation peaks to the previously assigned ^{1}H NMR spectrum, on the vertical axis.

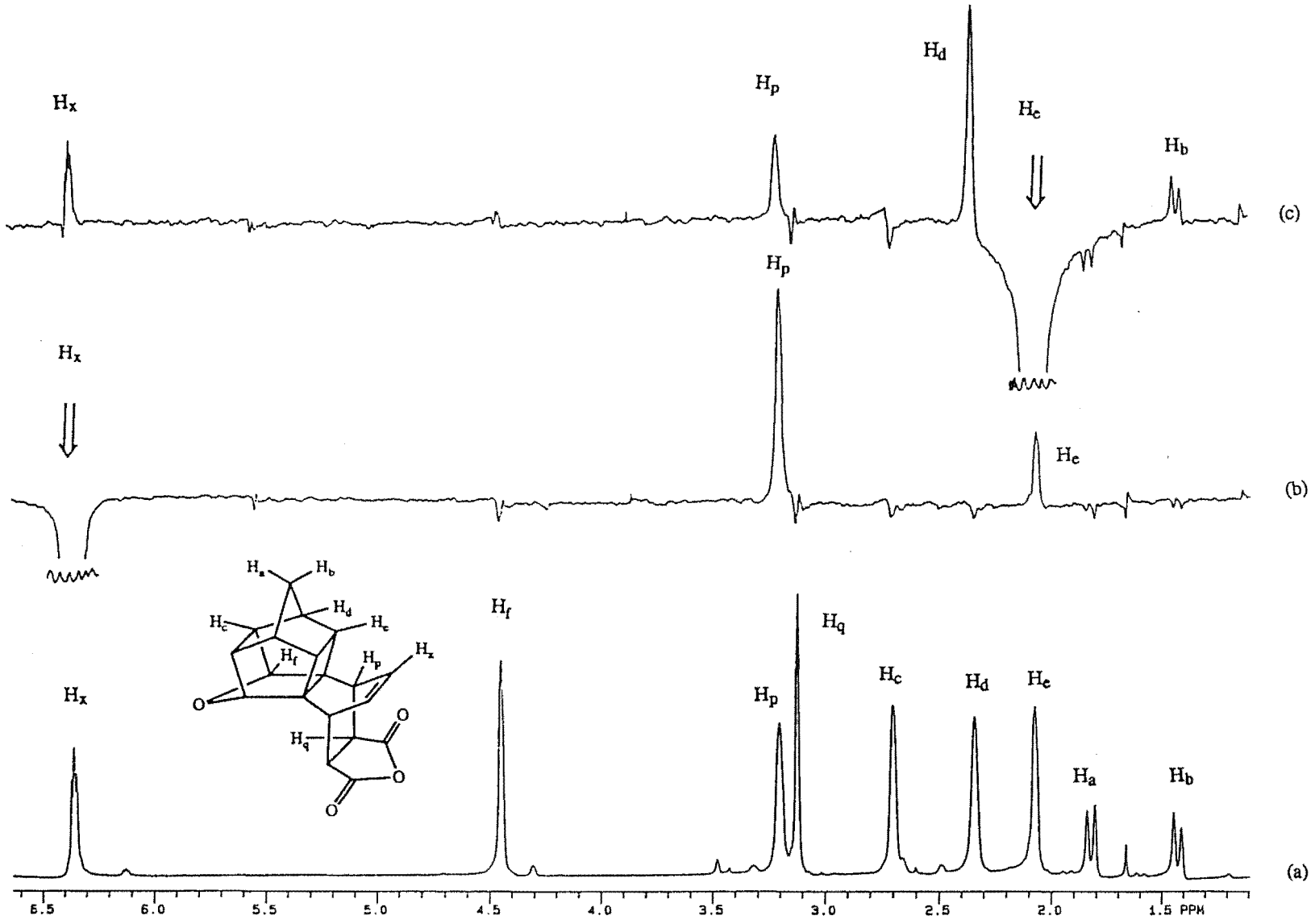
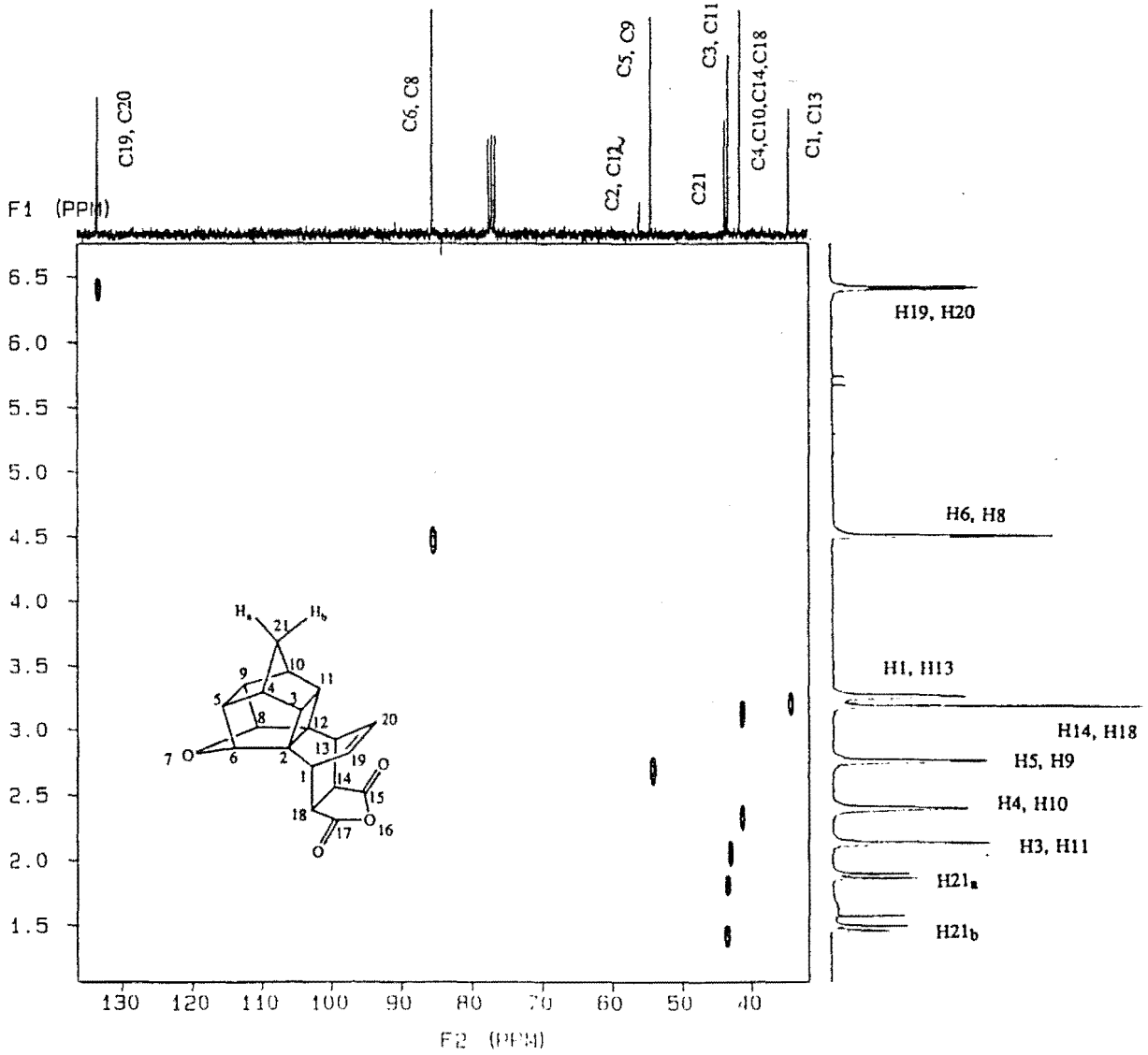


Figure 4.3. (a) Normal and (b, c) NOE difference ^{1}H NMR spectra for the ether-maleic anhydride adduct, **151**.

Figure 4.4. ^{1}H-^{13}C Heteronuclear correlated (HETCOR) NMR spectrum of the ether-maleic anhydride adduct, **151**.



2.1.1 Syntheses and photolyses of Diels-Alder adducts

Reduction of 1,4-dihydroxyanthraquinone with sodium borohydride

To a stirred solution of 1,4-dihydroxyanthraquinone (1g, 4.16 mmole) in methanol (50 mL) was added portionwise sodium borohydride (314 mg, 8.30 mmole) and the mixture was stirred at room temperature for 5 hours. The reaction mixture was acidified with dilute hydrochloric acid (5% v/v, 10 mL) and left overnight at room temperature. The product, an orange solid, precipitated out of the reaction mixture. The solution was further reduced in volume and the solid was filtered. The crude product was dissolved in ether and washed with potassium hydroxide solution (1% w/v, 50 mL), water (50 mL) and dried over magnesium sulphate. Removal of the solvent gave 1,4-anthraquinone **46**: mp 215-218°C (lit.[63] 219-223°C). ^{1}H NMR ($CDCl_3$) δ 7.08 (s, H2,H3); 7.70 (m, H6,H7); 8.07 (m, H5,H8); 8.62 (s, H9,H10).

Diels-Alder reactions of cyclopentadiene

(i) with 1,4-naphthoquinone

Freshly cracked cyclopentadiene (15 mL, 220 mmole) was added to a solution of 1,4-naphthoquinone (15 g, 95 mmole) in benzene (100 mL) and the mixture was stirred at 0-5°C for 4 hours. The solvent was removed under reduced pressure and the residue was recrystallised from petroleum ether to give *endo*-tetracyclo[10.2.1.$0^{2,11}$.$0^{4,9}$]-pentadeca-4,6,8,13-tetraene-3,10-dione **44** as white crystals. ^{1}H NMR ($CDCl_3$) δ 1.55 (m, H15); 3.46 (m, H1,H12); 3.65 (m, H2,H11); 5.98 (m, H13,H14); 7.69 (m, H5,H8); 8.02 (m, H6,H7); ^{13}C NMR ($CDCl_3$) δ 49.1 (C15); 49.4 (C1,C12,C2,C11); 126.8 (C13,C14); 134.0 (C5,C8); 135.5 (C6,C7); 135.8 (C4,C9); 197.7 (C3,C8).

(ii) with 1,4-anthraquinone **46**

Freshly cracked cyclopentadiene (130mg, 2.0 mmole) was added to a solution of 1,4-anthraquinone (222 mg, 1.06 mmole) in benzene (25 mL). The reaction mixture was stirred at 0-5°C for an hour and was allowed to warm up to room temperature and stirred overnight. Removal of the solvent gave a residue which was recrystallised from acetone to give the cyclopentadiene-1,4-anthraquinone adduct **47**: mp 166-167°C (lit.[64] 167-

168°C). ^{1}H NMR ($CDCl_3$) δ 1.60 (br s, H19); 3.52 (m, H1,H16); 3.69 (m, H2,H11); 5.99 (m, H18,H19); 7.67 (m, H7,H10); 8.03 (m, H5,H12).

Epoxidation of cyclopentadiene-naphthoquinone adduct 44

m-Chloroperbenzoic acid (3.90 g, 22.6 mmole) was added slowly to a solution of cyclopentadiene-naphthoquinone adduct **44** (3.00 g, 13.4 mmole) in dichloromethane (60 mL) at 0°C. When the addition was completed, the reaction mixture was allowed to warm up to room temperature and stirred for 3 days. The solid by-product, m-chlorobenzoic acid was filtered and washed with dichloromethane (20 mL). The filtrate was washed with sodium bicarbonate solution (5% w/v, 2 x 50 mL), water (2 x 50 mL) and dried over sodium sulphate. Removal of the solvent gave *exo*-14-oxapentacyclo[10.3.1.$0^{2,11}$.$0^{4,9}$.$0^{13,15}$]hexadeca-4,6,8-triene-3,10-dione **49** (2.97 g). ^{1}H NMR ($CDCl_3$) δ 0.95 (d, J = 10.5 Hz, H16b); 1.55 (d, J = 10.4 Hz, H16a); 3.00, 3.32 (br s, H1,H12,H2,H11,H13,H15); 7.76 (m, H5,H8); 8.08 (m, H6,H7); ^{13}C NMR ($CDCl_3$) δ 25.4 (C16); 42.8 (C1,C12); 48.7, 49.9 (C2,C11,C13,C15); 126.1 (C5,C8); 134.5 (C6,C7); 135.9 (C4,C9); 196.9 (C3,C10).

Photolysis of cyclopentadiene-1,4-naphthoquinone adduct 44

The Diels-Alder adduct **44** (10.0 g) in benzene (1L) was irradiated with a low-pressure 450W mercury lamp (Hanovia) for 10 hours. The solvent was removed under reduced pressure to give a residue which was recrystallised from petroleum ether to give a white solid, hexacyclo[10.2.1.$0^{2,11}$.$0^{4,9}$.$0^{4,14}$.$0^{9,13}$]pentadeca-5,7-diene-3,10-dione **35**: mp 110-112°C (lit.[57a] 111-112°C); IR (KBr) 1740 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 1.76 (d, J = 11.4 Hz, H15b); 1.99 (d, J = 11.3 Hz, H15a); 2.80 (br s, H2,H11); 3.00 (br s, H1,H12); 3.35 (br s, H13,H14); 5.39 (m, H5,H8); 5.98 (m, H6,H7); ^{13}C NMR ($CDCl_3$) δ 38.9 (C15); 44.2 (C1,C12); 50.1 (C4,C9); 51.6 (C13,C14); 54.4 (C2,C11); 119.7 (C5,C8); 124.6 (C6,C7); 211.1 (C3).

Attempted photolysis of cyclopentadiene-1,4-anthraquinone adduct 47

The Diels-Alder adduct of cyclopentadiene and 1,4-anthraquinone (65.5 mg) in acetone (5 mL) was irradiated with a low-pressure 450W mercury lamp (Hanovia). Monitoring by ^{1}H NMR indicated that the reaction mixture remained unchanged. The

photolysis was stopped after 9 hours. The solvent was removed under reduced pressure to give a residue which was shown by ^{1}H NMR to be unreacted adduct **47**.

Attempted photolysis of *exo*-epoxide 49

Solutions of *exo*-epoxide **49** (100 mg) in hplc grade acetonitrile (100 mL) were irradiated in a Rayonet reactor at 253.7 nm, 300 nm or 350 nm. The reactions were followed by ^{1}H NMR analysis of the reaction mixtures. After 12 hours when no reaction was apparent, the photolysis was stopped. Removal of the solvent and examination of the residues by ^{1}H NMR revealed either unreacted starting material or, in the case of irradiation at 253.7 nm, an intractable mixture of unidentifiable product(s) and unreacted epoxide.

2.1.2 Syntheses of monoacetal 52 and thioacetal 53

Synthesis of monoethylene acetal 52

A mixture of the diketone **35** (1.5 g), ethylene glycol (1 mL), p-toluenesulphonic acid (125 mg) and benzene (30 mL) was heated under reflux with azeotropic distillation of water/benzene for 5 hours. The reaction mixture was then cooled and poured into ice-cooled sodium carbonate solution (10%w/v, 50 mL) and extracted with dichloromethane (50 mL, 4 x 25 mL). The combined extracts were dried over sodium sulphate and the solvent removed to give a residue (1.74 g). Recrystallisation from methanol gave hexacyclo[10.2.1.$0^{2,11}$.$0^{4,9}$.$0^{4,14}$.$0^{9,13}$]pentadeca-5,7-diene-3,10-dione monoethylene acetal **52** (1.61 g, 90%): mp 128-129°C; IR (KBr) 3060, 3000, 2900, 1730 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 1.43 (d, J = 11.2 Hz, H15b); 1.79 (d, J = 11.2 Hz, H15a); 2.55 (m, H2,H11); 2.67 (br s, $W_{h/2}$ = 10 Hz, H1); 2.86 (br s, $W_{h/2}$ = 10 Hz, H12); 2.97 (m, H14); 3.10 (m, H13); 3.94 (m, ethylene acetal); 5.49 (m, H5,H8); 5.89 (m, H6,H7); ^{13}C NMR ($CDCl_3$) δ 36.7 (C15); 42.6 (C1); 45.2 (C12); 47.2 (C4); 49.8 (C14); 50.8 (C2); 50.9 (C9); 53.3 (C11); 54.4 (C13); 65.7, 65.9 (ethylene acetal); 113.6 (C10); 120.8 (C5); 122.3 (C8); 123.6 (C6,C7); 212.7 (C3); HRMS requires for $C_{17}H_{16}O_3$ ($M^{+\cdot}$): 268.1099, found: 268.1096. Anal. calcd for $C_{17}H_{16}O_3$: C, 76.10%; H, 6.01%. Found: C, 76.30%; H, 5.94%.

Synthesis of monoethylene thioacetal 53

A mixture of the diketone **35** (1 g, 4.46 mmole), ethane dithiol (0.375 mL, 4.46 mmole) and boron trifluoride etherate (1.1 mL) was stirred in ethyl acetate (25 mL) at room temperature for 1 day. A solid by-product **54** (238 mg) which precipitated out of the reaction mixture was filtered and washed with ethyl acetate (2 x 25 mL). ^{1}H NMR analysis of **54** showed broadening of peaks indicative of a dynamic process occuring on the NMR time scale. The identity of this compound is most likely the hemithioacetal **54**; IR (KBr) 3400, 1730 cm^{-1}. Water (15 mL) was added to the filtrate and the ethyl acetate layer was separated and washed with a saturated solution of sodium bicarbonate (2 x 10 mL) and water (3 x 10 mL). The extract was dried over sodium sulphate and the solvent was removed to give a residue (1.03 g). ^{1}H NMR analysis of this residue indicates the presence of two unsymmetrical cage products, one of which was **54**. The residue was adsorbed onto silica on a radial chromatograph and elution with a mixture of ether and petroleum ether (1:19) gave hexacyclo-[10.2.1.$0^{2,11}$.$0^{4,9}$.$0^{4,14}$.$0^{9,13}$]pentadeca-5,7-diene-3,10-dione monoethylene thioacetal **53** (570 mg, 43%) which was recrystallised from benzene: mp 154-155°C; IR (KBr) 1740, 1600 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 1.41 (d, J = 11.2 Hz, H15b); 1.85 (d, J = 11.0 Hz, H15a); 2.67 (m, H1,H2); 2.90 (m, H12,H14); 3.04 (m, H11); 3.22 (m, 5H, H13,ethylene thioacetal); 5.55 (m, H5); 5.82 (m, H8); 5.96 (m, H6,H7); ^{13}C NMR ($CDCl_3$) δ 36.3 (C15); 39.4, 40.0 (ethylene thioacetal); 43.1 (C1); 48.3 (C14); 49.1 (C12); 50.6, 56.7 (C4,C9); 53.32, 61.4 (C2,C11); 56.3 (C13); 77.5 (C10); 121.3 (C5); 123.8 (C6); 124.4 (C7); 125.5 (C8); 214.2 (C3); HRMS requires for $C_{17}H_{16}S_2O$ ($M^{+\cdot}$): 300.0643, found: 300.0649. Anal. calcd for $C_{17}H_{16}S_2O$: C, 67.96%; H, 5.37%. Found: C, 68.04%; H, 5.11%.

Dehydration of the hemithioacetal 54

A mixture of hemithioacetal **54** (210 mg) and p-toluenesulphonic acid (12 mg) was heated under reflux in benzene (10 mL) for 7 hours with azeotropic distillation of water/benzene using a Dean and Stark trap. The reaction mixture was cooled and poured into sodium carbonate solution (10% w/v, 10 mL). The benzene layer was separated, washed with water (2 x 10 mL) and dried over sodium sulphate. Removal of the solvent gave a residue (160 mg); ^{1}H NMR analysis of the residue revealed a mixture of thioacetal

53 and unreacted hemithioacetal **54**. Recrystallisation of this residue from benzene gave thioacetal **53** (39 mg), identical to an authentic sample.

Attempted syntheses of mixed thione-ketone 55

(i) with hydrogen sulfide in trifluoroacetic acid

Hydrogen sulfide was bubbled through a stirred solution of cage diketone **35** (200 mg) in trifluoroacetic acid (3 mL) for 2 hours at room temperature. The reaction mixture was extracted with dichloromethane (3 x 20 mL) and washed with sodium bicarbonate solution (1% w/v, 10 mL), water (20 mL) and dried over sodium sulphate. Removal of the solvent gave a residue which was shown by ^{1}H NMR spectral analysis to be unreacted diketone **35** and trace amounts of an unidentified aromatic rearrangement compound.

(ii) with Lawesson Reagent

Cage diketone **35** (100 mg, 0.45 mmole) and 2,4-(bis-4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane-2,4-disulfide (Lawesson Reagent) (90 mg, 0.22 mmole) were heated under reflux in a 1:1 mixture of benzene and toluene (5 mL) for 15 hours. Removal of the solvent gave a residue, the ^{1}H NMR spectrum of which indicated unreacted starting materials.

(iii) with tetraphosphorus decasulfide

Sodium bicarbonate (227 mg, 2.70 mmole) was added slowly to a mixture of cage diketone **35** (100 mg, 0.45 mmole) and tetraphosphorus decasulfide (298 mg, 0.67 mmole) in diglyme (5 mL). The reaction mixture was stirred and heated at 120°C for 15 hours. The reaction mixture was cooled and poured into water (10 mL) and extracted with dichloromethane (3 x 25 mL). The combined extracts were washed with water (2 x 20 mL) and dried over sodium sulphate. Removal of the solvent gave a residue, the ^{1}H NMR spectrum of which indicated an intractable mixture but with the diene moiety absent.

2.1.3 Reduction of 52 and subsequent transannular reactions

Reduction of monoethylene acetal 52

(i) with sodium borohydride and cerium chloride.

To a solution of monoacetal **52** (1.8 g, 6.72 mmole) and cerium chloride heptahydrate (5 g, 13.42 mmole) in methanol (60 mL) was added slowly sodium borohydride (0.504 g, 13.32 mmole). The reaction mixture was stirred at room temperature for 2 hours. The reaction mixture was quenched with water (20 mL) and extracted with dichloromethane (50 mL, 4 x 25 mL) and dried over sodium sulphate. The solvent was removed under reduced pressure to give a solid (1.465 g); ^{1}H NMR analysis of the solid showed the presence of only one product. The solid was recrystallised from methanol to give 10-*endo*-hydroxyhexacyclo[10.2.1.$0^{2,11}$.$0^{4,9}$.$0^{4,14}$.$0^{9,13}$]pentadeca-5,7-diene-3-one ethylene acetal **56**: mp 79-80°C; IR (KBr) 3430, 1580 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 1.02 (d, J = 10.8 Hz, H15b); 1.55 (d, J = 10.8 Hz; H15a); 2.26 (m, H11); 2.44 (m, H1); 2.50 (m, H2); 2.61 (m, H12); 2.75 (m, H14); 2.84 (m, H13); 3.47 (dd, $J_{H10,OH}$ = 12.3 Hz, $J_{H10,H11}$ = 2.9 Hz, H3); 4.03 (m, ethylene acetal); 5.34 (d, $J_{OH,H10}$ = 12.1 Hz, OH); 5.49 (m, H5,H8); 5.88 (m, H6,H7); ^{13}C NMR ($CDCl_3$) δ 32.9 (C15) 43.1 (C1); 44.7 (C12); 47.1 (C2); 47.4 (C11); 48.1, 48.4 (C4,C9); 53.1 (C14); 54.0 (C13); 64.4, 66.3 (ethylene acetal); 76.1 (C3); 115.4 (C10); 122.6, 128.5 (C5,C8); 123.1, 124.1 (C6,C7); HRMS requires for $C_{17}H_{18}O_3$ ($M^{+\cdot}$): 270.1256, found: 270.1250. Anal. calcd for $C_{17}H_{18}O_3$: C, 75.53%; H, 6.71%. Found: C, 75.31%; H, 6.61%.

(ii) with lithium aluminium hydride.

A suspension of lithium aluminium hydride (20 mg, 0.52 mmole) in 2 mL of dry ether was added slowly to a solution of monoethylene acetal **52** (100 mg, 0.37 mmole) in dry ether (5 mL). The reaction mixture was heated under reflux for 2 hours. The reaction mixture was cooled and the excess lithium aluminium hydride was decomposed with aqueous ammonium chloride and extracted with ether (3 x 10 mL). The combined ether extracts were washed with water (2 x 5 mL) and dried over magnesium sulphate. Removal of the solvent gave a solid which was shown by NMR spectroscopy to be the

endo-hydroxy monoacetal **56**. ^{1}H and ^{13}C NMR spectra of this solid were identical to the product from sodium borohydride reduction of the monoethyleneacetal **52**.

Transannular cyclisation of the *endo*-hydroxy-monoethylene acetal 56

A solution of **56** in chloroform or pyridine was left standing at room temperature for four weeks. Removal of the solvent gave 12-(2-hydroxyethoxy)-13-oxaheptacyclo-[8.5.1.$0^{2,9}$.$0^{3,8}$.$0^{3,14}$.$0^{8,12}$.$0^{11,15}$]hexadeca-4,6-diene **57** which was recrystallised from petroleum ether-dichloromethane: mp 87-88°C; IR (KBr) 3455, 1585, 1470 cm^{-1}. ^{1}H NMR ($CDCl_3$) 1.44 (d, J = 10.6 Hz, H16b); 1.83 (d, J = 10.6 Hz, H16a); 2.58 (m, H1,H10); 2.75 (br s, $W_{h/2}$ = 20 Hz, OH); 2.87 (m, H2,H9,H11,H15); 3.75, 3.90 (br s, m, 4H, $OC\underline{H_2}C\underline{H_2}OH$); 4.41 (d, $J_{H14,H15}$ = 4.5 Hz, H14); 5.55 (m, H4,H7); 5.78 (m, H5,H6); ^{13}C NMR ($CDCl_3$) 41.7 (C16); 42.5, 44.6 (C1,C10); 51.4, 55.4 (C11,C15); 52.0, 54.0 (C3,C8); 53.8, 53.9 (C2,C9); 62.3, 68.0 (OCH_2CH_2OH); 86.8 (C14); 121.8, 124.1 (C4,C7); 122.7 (C12); 123.0, 123.1 (C5,C6). HRMS requires for $C_{17}H_{18}O_3$ ($M^{+\cdot}$): 270.1256, found: 270.1254. Anal. calcd for $C_{17}H_{18}O_3$: C, 75.53%; H, 6.71%. Found: C, 75.24%; H, 7.02%.

Acetylation of 57

A solution of **57** (82 mg) and acetic anhydride (110 mg) in pyridine (2 mL) was heated at *ca.* 60°C for 2 hours. The reaction mixture was cooled and poured into aqueous hydrochloric acid solution (7% v/v, 25 mL) and extracted with dichloromethane (2 x 15 mL). The combined extracts were washed with sodium bicarbonate solution (1% w/v, 25 mL), water (2 x 20 mL) and dried over magnesium sulphate. Removal of the solvent gave 12-(2-acetoxyethoxy)-13-oxaheptacyclo[8.5.1.$0^{2,9}$.$0^{3,8}$.$0^{3,14}$.$0^{8,12}$.$0^{11,15}$]-hexadeca-4,6-diene **58**. ^{1}H NMR ($CDCl_3$) 1.43 (d, J = 10.7 Hz, H16b); 1.82 (d, J = 10.7 Hz, H16a); 2.08 (s, CH_3); 2.58, 2.84 (m, 6H, H1,H2,H9,H10,H11,H15); 3.93, 4.25 (m, $OC\underline{H_2}C\underline{H_2}OAc$); 4.41 (d, $J_{H14,H15}$ = 4.7 Hz, H14); 5.55 (m, H4,H7); 5.78 (m, H5,H6); ^{13}C NMR ($CDCl_3$) 20.9 (CH_3); 41.7 (C16); 42.5, 44.7, 50.1, 50.7, 53.9, 55.5 (C1,C2,C9,C10,C11,C15); 52.0 (C3,C8); 63.7, 64.0 ($O\underline{C}H_2\underline{C}H_2OAc$); 87.0 (C14); 122.0, 124.1 (C4,C7); 122.8 (C12); 123.0 (C5,C6); 171.0 (acetyl carbonyl).

Hydrolysis of *endo*-hydroxy-monoethylene acetal 56

endo-Hydroxy-monoethylene acetal **56** (500 mg) was dissolved in a mixture of aqueous hydrochloric acid (6% v/v, 20 mL) and tetrahydrofuran (3 mL) and the mixture was heated at 50°C for 2 hours. The reaction mixture was cooled and neutralised with sodium bicarbonate. Water (10 mL) was added and the reaction mixture was extracted with dichloromethane (3 x 30 mL). The combined extracts were dried over magnesium sulphate and removal of the solvent gave a solid. ^{1}H NMR analysis of the solid showed the absence of the acetal moiety, and the presence of the diene moiety and methylene protons of the norbonyl moiety. The resonance signals between 2.0 - 5.5 ppm in the spectrum showed extensive broadening, typical of an equilibrium between two compounds. The spectral evidence is consistent with (i) the successful hydrolysis of the acetal moiety to a carbonyl group and (ii) cyclisation involving the *endo*-hydroxy group and the transannular carbonyl group to give an equilibrium mixture of the *endo*-hydroxy ketone **59a** and the bridged hemiacetal **59b**. A sample of the solid was adsorbed onto silica and elution with ether gave a solid; the ^{1}H NMR spectrum showed sharpened peaks for the *endo*-hydroxyketone **59a** and bridged hemiacetal **59b**. ^{1}H NMR ($CDCl_3$) of the mixture; δ 1.35, 1.42, 1.79, 1.82 (d, H15 of **59a**; H16 of **59b**); 2.15, 3.28 (br s, $W_{h/2}$ = 15 Hz, $W_{h/2}$ = 9 Hz, OH of **59a** and **59b**); 2.5 - 3.1 (12H, CH of norbonyl moieties of **59a** and **59b**); 3.82 (d, $J_{H10,H11}$ = 3.3 Hz, C<u>H</u>OH, H10 of **59a**); 4.41 (d, $J_{H12,H11}$ = 4.9 Hz, C<u>H</u>-O-COH, H12 of **59b**); 5.3 - 6.0 (8H, diene moieties of **59a** and **59b**). ^{13}C NMR ($CDCl_3$) for **59a**, δ 36.4 (C15); 41.8, 43.9, 49.5, 52.6, 54.9, 55.8 (C1,C2,C11,C12,C13,C14); 76.0 (C10); 122.1, 123.7, 125.0, 125.4 (C5,C6,C7,C8). ^{13}C NMR ($CDCl_3$) for **59b**, δ 41.7 (C16); 42.4, 44.6, 50.8, 54.0, 54.6, 56.9 (C1,C2,C9,C10,C11,C15); 87.3 (C12); 119.8 (C14); 119.9, 122.8, 124.8, 125.3 (C4,C5,C6,C7).

Hydrolysis of bridged hemiacetal 57

The hemiacetal **57** was hydrolysed in the same manner as previously described and ^{1}H NMR analysis of the crude product was identical to the previous case, indicating

the formation of an equilibrium mixture of the *endo*-hydroxyketone **59a** and hemiacetal **59b**.

2.1.4 Reactions of diketone 35 with alcohols.

(i) methanol

A solution of cage diketone **35** (150 mg, 0.67 mmole) and p-toluenesulfonic acid (37.5 mg) in dry methanol (10 mL) was heated under reflux for 5 hours. The solvent was removed and the residue was dissolved in sodium carbonate solution (10% w/v, 10 mL), extracted with dichloromethane (3 x 25 mL) and dried over sodium sulphate. The solvent was removed to give a crude product (193 mg) which was adsorbed onto silica on a radial chromatograph. Elution with a mixture of ether-petroleum ether (3:7) gave hexacyclo[10.2.1.$0^{2,11}$.$0^{4,9}$.$0^{4,14}$.$0^{9,13}$]pentadeca-5,7-diene-3,10-dione dimethoxy acetal **64** (155 mg, 84%) which was recrystallised from methanol as colourless crystals: mp 90-91°C; IR (KBr) 1730, 1570, 1030 cm^{-1}. ^1H NMR (DMSO) δ 1.37 (d, J = 10.8 Hz, H15b); 1.78 (d, J = 10.8 Hz, H15a); 2.49 (m, H2); 2.64 (m, H12); 3.01 (m, H14,H11,H13); 3.11 (s, *exo*-OCH_3); 3.28 (s, *endo*-OCH_3); 5.56 (d, J = 9.0 Hz, H5); 5.88 (m, H8), 5.88, 6.03 (m, H6,H7); ^{13}C NMR (DMSO) δ 35.7 (C15); 41.8 (C1); 43.8 (C12); 45.9, 50.9 (C4,C9); 48.1 (*endo*-OCH_3); 49.5 (C2); 49.8 (*exo*-OCH_3); 50.0 (C11); 51.2 (C14); 56.0 (C13); 105.6 (C10); 121.0, 123.4, 125.0 (C6,C7,C8); 121.4 (C5); 210.9 (C3); HRMS requires for $C_{17}H_{18}O_3$ ($M^{+\cdot}$): 270.1256, found: 270.1252. Anal. calcd for $C_{17}H_{18}O_3$: C, 75.53%; H, 6.71%. Found: C, 75.80%; H, 6.83%.

(ii) ethanol

(a) at room temperature. Cage diketone **35** (1 g) was dissolved in a 1:1 mixture of dichloromethane-ethanol (5 mL) and the solution was left standing at room temperature for 4 days. The product, the mono-hemiacetal of ethanol **37** (0.45 g) crystallised from the solution: mp 110-113°C. ^1H NMR (DMSO) δ 1.00 (t, $OCH_2\underline{CH_3}$); 1.34 (d, J = 10.8 Hz, H15b); 1.73 (d, J = 10.7 Hz, H15a); 2.44 (m, 1H); 2.60 (m, 1H); 2.77 (m, 2H); 2.89 (m, 1H); 3.00 (m, H14); 3.51 (m, $O\underline{CH_2}CH_3$); 5.47, 5.78 (d, J = 9.6 Hz, J = 10.0 Hz, H5,H8); 5.90 (m, H6,H7); ^{13}C NMR (DMSO) δ 15.0 ($OCH_2\underline{C}H_3$); 35.8

(C15); 41.9, 45.0 (C1,C12); 46.1, 51.7 (C4,C9); 49.6, 49.9 (C13,C14); 55.3, 55.6 (C2,C11); 58.0 ($O\underline{C}H_2CH_3$); 102.4 (C10); 121.5, 121.6, 123.3, 124.9 (C5,C6,C7,C8); 121.0 (C3).

(b) at 80°C in benzene catalysed by p-toluenesulphonic acid. A mixture of cage diketone **35** (500 mg), ethanol (2 mL) and p-toluenesulphonic acid (125 mg) was heated under reflux in benzene (30 mL) for 5 hours. The reaction mixture was cooled and poured into a solution of sodium carbonate (10% w/v, 30 mL). The benzene layer was washed with water (2 x 20 mL) and dried over magnesium sulphate. Removal of the solvent gave a solid; ^{1}H NMR spectral analysis revealed its identity as the unreacted diketone **35**.

(iii) isopropanol

A solution of cage diketone **35** (300 mg, 1.34 mmole) and p-toluenesulphonic acid (37.5 mg) was heated at 40°C in dry isopropanol (7.5 mL) for 6 days. Water (20 mL) and sodium carbonate solution (10% w/v, 20 mL) were added to the reaction mixture and it was extracted with dichloromethane (3 x 20 mL). The combined extracts were washed with water (20 mL) and dried over sodium sulphate. The solvent was removed under reduced pressure to give a residue (266 mg), which was adsorbed onto silica on a radial chromatograph. Elution with a mixture of ether-petroleum ether (1:4) gave 13-oxa-12,14-diisopropoxyheptacyclo[8.5.1.$0^{2,9}$.$0^{3,8}$.$0^{3,14}$.$0^{8,12}$.$0^{11,15}$]hexadeca-4,6-diene **66** (11 mg): mp 53-54°C; IR (KBr) 1456, 1369, 1331, 1116 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 1.20 (m, 12H, 4 x CH_3); 1.38 (d, J = 10.5 Hz, H16b); 1.75 (d, J = 10.51 Hz, H16a); 2.58 (br s, $W_{h/2}$ = 7.5 Hz, H1,H10); 2.79 (br s, $W_{h/2}$ = 7.5 Hz, H2,H9); 2.90 (br s, $W_{h/2}$ = 6.0 Hz, H11,H15); 4.15 (m, 2 X $O\underline{C}H(CH_3)_2$); 5.53 (m, H4,H7); 5.78 (m, H5,H6); ^{13}C NMR ($CDCl_3$) δ 23.8, 24.1 (4 x CH_3); 41.7 (C16); 43.4 (C1,C10); 53.6 (C3,C8); 53.8 (C2,C9); 54.4 (C11,C15); 68.7 (2 x $O\underline{C}H(CH_3)_2$); 116.7 (C12,C14); 121.8 (C4,C7); 122.9 (C5,C6); HRMS requires for $C_{21}H_{26}O_3$ ($M^{+\cdot}$): 326.1883, found: 326.1881. Anal. calcd for $C_{21}H_{26}O_3$: C, 77.27%; H, 8.03%. Found: C, 76.83%; H, 8.27%.

Further elution gave hexacyclo[10.2.1.$0^{2,11}$.$0^{4,9}$.$0^{4,14}$.$0^{9,13}$]pentadeca-5,7-diene-3,10-dione diisopropoxy acetal **65** (67 mg) which was recrystallised from ether-petroleum ether; mp: 108-109°C; IR (KBr) 1736, 1454, 1383, 1148, 1042 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.97 (d, J = 6.2 Hz, CH_3); 1.09 (d, J = 6.1 Hz, CH_3); 1.17 (d, J = 6.2 Hz, CH_3); 1.22 (d, J = 6.1 Hz, CH_3); 1,27 (d, J = 11.1 Hz, H15b); 1.69 (d, J = 11.0 Hz, H15a); 2.49, 2.81 (m, H13,H14); 2.61, 2.81 (m, H1,H12); 2.81,3.08 (m, H2,H11); 3.86, 4.18 (m, OC<u>H</u>$(CH_3)_2$); 5.56, 5.87 (d, J = 9.51 Hz, J = 9.73 Hz, H5,H8); 5.78, 5.92 (m, H6,H7); ^{13}C NMR ($CDCl_3$) δ 22.9, 24.4, 24.9 (CH_3); 35.5 (C15); 42.5, 44,4 (C1,C12); 50.3, 50.4 (C13,C14); 52.4 (C4,C9); 54.5 (C2); 57.6 (C11); 63.9, 67.1 (O<u>C</u>H$(CH_3)_2$); 106.1 (C10); 121.3 (C5); 121.5, 123.8 (C6,C7); 125.1 (C8); 212.4 (C3); HRMS requires for $C_{21}H_{26}O_3$ ($M^{+\cdot}$): 326.1882, found: 326.1885. Further elution with ether-petroleum ether (7:3) gave unreacted cage diketone **35** (77 mg).

2.2 Diels-Alder reactions of the monoethylene acetal diene 52.

(i) A solution of **52** (500 mg) and maleic anhydride **38** (183 mg) in benzene (10 mL) was heated under reflux for 1 day. The product 15-oxaoctacyclo-[10.5.2.$1^{5,8}$.$0^{2,6}$.$0^{2,11}$.$0^{4,9}$.$0^{7,11}$.$0^{13,17}$]eicos-18-ene-3,10,14,16-tetraone-10-ethylene acetal **75** crystallised from the reaction mixture as white needles (567 mg): mp 272-273°C; IR (KBr) 1870, 1850, 1780, 1750 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.52 (d, J = 11.2 Hz, H20b); 1.80 (d, J = 11.2 Hz, H20a); 2.28 (m, H6); 2.48 (m, H7,H4); 2.64 (m, H5,H9,H8); 3.30 (H1); 3.40 (m, H12); 3.51 (m, H13); 3.63 (m, H17); 4.00 (m, ethylene acetal); 6.49 (m, H19,H18); ^{13}C NMR ($CDCl_3$) δ 32.4 (C1), 32.7 (C12); 39.0 (C20); 39.8 (C6); 40.3 (C17); 40.7 (C13); 42.0 (C5); 43.5 (C8); 44.3 (C7); 49.3 (C2); 51.4 (C4); 51.7 (C11); 54.2 (C9); 64.9, 65.4 (ethylene acetal); 113.1 (C10); 132.6 (C19); 134.0 (C18); 172.6, 173.2 (C14,C16); 212.5 (C3); HRMS requires for $C_{21}H_{18}O_6$ ($M^{+\cdot}$): 366.1103, found: 366.1090. Anal. calcd for $C_{21}H_{18}O_6$: C, 68.85%; H, 4.95%. Found: C, 68.70%; H, 5.09%.

(ii) A solution of **52** (100 mg) and 1,4-benzoquinone **39** (81 mg) in toluene (10 mL) was heated under reflux for 5 days. The product octacyclo-[10.6.2.$1^{5,8}$.$0^{2,6}$.$0^{2,11}$.$0^{4,9}$.$0^{7,11}$.$0^{13,18}$]heneicos-15,19-diene-3,10,14,17-tetraone-10-ethylene acetal **77** crystallised from the reaction mixture (65 mg): mp 235-237°C dec.; IR (KBr) 1730, 1680 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.48 (d, J = 11.0 Hz, H21b); 1.77 (d, J = 11.0 Hz, H21a); 2.23 (m, H6); 2.45 (m, H4,H7); 2.62 (m, H9,H5,H8); 3.39 (m, H1,H13); 3.49 (m, H12,H18); 3.99 (m, ethylene acetal); 6.39 (m, H20,H19); 6.64 (dd, J = 9.8 Hz, J = 10.3 Hz, H15,H16); ^{13}C NMR ($CDCl_3$) δ 34.8 (C1); 35.3 (C12); 38.9 (C21); 39.9 (C6); 42.0 (C5); 43.4 (C8); 44.2 (C13); 44.3 (C18); 44.4 (C7); 49.9 (C2); 51.7 (C4); 51.9 (C11); 54.8 (C9); 65.2, 65.6 (ethylene acetal); 113.5 (C10); 133.4 (C20); 134.8 (C19); 141.4, 141.8 (C15,C16); 198.6, 199.3 (C14,C17); 213.5 (C3); HRMS requires for $C_{23}H_{20}O_5$ ($M^{+\cdot}$): 376.1311, found: 376.1309. Anal. calcd for $C_{23}H_{20}O_5.1/4H_2O$: C, 72.52%; H, 5.42%. Found: C, 72.42%; H, 5.47%.

(iii) A solution of **52** (100 mg) and 1,4-naphthoquinone **71** (77 mg) in benzene (10 mL) was heated under reflux for 5 days. The product nonacyclo[10.10.2.$1^{5,8}$.$0^{2,6}$.-$0^{2,11}$.$0^{4,9}$.$0^{7,11}$.$0^{13,22}$.$0^{15,20}$]pentacos-15,17,19,23-tetraene-3,10,14,21-tetraone-10-ethylene acetal **79** crystallised from the reaction mixture (77 mg): mp 253-254°C; IR (KBr) 1730, 1670, 1580, 1470 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.50 (d, J = 11.0 Hz, H25b); 1.78 (d, J = 11.0 Hz, H25a); 2.26 (m, H6); 2.48 (m, H7,H4); 2.65 (m, H5,H9,H8); 3.55 (m, H1); 3.68 (m, H12,H13,H22); 3.94, 4.07 (m, ethylene acetal); 6.34 (m, H24); 6.43 (m, H23); 7.69 (m, H16,H19); 8.00 (m, H17,H18); ^{13}C NMR ($CDCl_3$) δ 34.6 (C1); 35.4 (C12); 38.9 (C6); 39.9 (C25); 42.0 (C5); 43.4 (C8); 44.4 (C7); 45.3 (C13,C22); 50.1 (C2); 51.8 (C4); 52.0 (C11); 54.9 (C9); 65.2, 65.7 (ethylene acetal); 113.6 (C10); 126.5, 126.9 (C16,C19); 133.8 (C24); 133.8, 134.0 (C17,C18); 135.3 (C23); 135.3, 135.8 (C15,C20); 197.0, 197.8 (C14,C21); 213.7 (C25); HRMS requires for $C_{27}H_{22}O_5$ ($M^{+\cdot}$): 426.1467, found: 426.1468. Anal. calcd for $C_{27}H_{22}O_5.2/3H_2O$: C, 73.96%; H, 5.37%. Found: C, 73.84%; H, 5.77%.

(iv) A solution of **52** (300 mg) and methyl vinyl ketone **72** (2 mL) in benzene (15 mL) was heated under reflux for 7 weeks. The solvent was removed under reduced pressure to give a solid residue (490 mg), which was adsorbed onto silica on a radial chromatograph. Elution with ether-petroleum ether (1:1) gave unreacted monoacetal **52** (75 mg). Further elution gave 14-acetylheptacyclo[10.2.2.$1^{5,8}$.$0^{2,6}$.$0^{2,11}$.$0^{4,9}$.$0^{7,11}$]-heptadeca-15-ene-3,10-dionemonoethylene acetal **81** (143 mg), which was recrystallised from methanol: mp 153-154°C; IR (KBr) 1730, 1709 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.33 (m, H13d); 1.43 (d, J = 10.9 Hz, H17b); 1.71 (d, J = 10.8 Hz, H17a); 1.86 (m, H13c); 2.11 (s, CH_3); 2.19 (m, H6); 2.37 (m, H7,H4); 2.54 (m, H5,H9,H8); 2.70 (m, H12); 2.94 (m, H1); 3.11 (m, H14); 3.94 (m, 4H, ethylene acetal); 6.20 (m, H16); 6.43 (m, H15); ^{13}C NMR ($CDCl_3$) δ 23.7 (C13); 28.4 (CH_3); 31.6 (C12); 31.9 (C1); 39.0 (C17); 39.8 (C6); 41.9 (C5); 43.3 (C8); 44.6 (C7); 45.7 (C14); 51.0 (C2); 51.8 (C4); 52.5 (C11); 54.9 (C9); 65.1, 65.5 (ethylene acetal); 113.8 (C10); 130.7 (C16); 135.8 (C15); 209.8 (acetyl carbonyl); 214.7 (C3); HRMS requires for $C_{22}H_{21}O_4$ ($M^{+\cdot}$): 338.1518, found : 338.1515. Anal. calcd for $C_{22}H_{21}O_4$: C, 74.54%; H, 6.55%. Found: C, 74.43%; H, 6.57%.

Further elution with ether-petroleum ether (7:3) gave 13-acetylheptacylo-[10.2.2.$1^{5,8}$.$0^{2,6}$.$0^{2,11}$.$0^{4,9}$.$0^{7,11}$]heptadeca-15-ene-3,10-dione monoethylene acetal **82** (104 mg) which was recrystallised from methanol: mp 183-184°C; IR (KBr) 1735, 1701 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.44 (d, J = 10.9 Hz, H17b); 1.66 (m, H14a); 1.72 (d, J = 12.4 Hz, H17a); 2.02 (m, H14b); 2.03 (s, CH_3); 2.17 (m, H6); 2.43 (m, H4,H7); 2.51 (m, H5); 2.59 (m, H8,H1); 2.69 (m, H9); 3.01 (m, H13); 3.11 (m, H12); 3.97 (m, ethylene acetal); 6.26 (m, H15); 6.36 (m, H16); ^{13}C NMR ($CDCl_3$) δ 22.3 (C14); 28.2 (CH_3); 29.9 (C1); 33.5 (C12); 39.0 (C17); 40.2 (C6); 41.9 (C5); 43.2 (C1); 44.5 (C7); 46.2 (C13); 50.7 (C2); 51.8 (C4); 52.3 (C11); 54.6 (C8); 64.9, 65.4 (ethylene acetal); 113.8 (C10); 132.0 (C15); 134.6 (C16); 209.4 (acetyl carbonyl); 214.5 (C3); HRMS requires for $C_{22}H_{21}O_4$ ($M^{+\cdot}$): 338.1518, found: 338.1521. Anal. calcd for $C_{22}H_{21}O_4$: C, 74.54%; H, 6.55%. Found: C, 74.29%; H, 6.41%.

(v) A solution of **52** (200 mg) and dimethylacetylene dicarboxylate **40** (226 mg) in benzene (10 mL) was heated under reflux for 11 days. The solvent was removed under reduced pressure to give an oil, which was adsorbed onto silica on a radial chromatograph. Elution with ether-petroleum ether (1:1) gave 13,14-bis(methoxycarbonyl)heptacyclo[10.2.2.1^{5,8}.0^{2,6}.0^{2,11}.0^{4,9}.0^{7,11}]heptadeca-13,15-diene-3,10-dione monoethylene acetal **86** (122 mg) which was recrystallised from benzene: mp 156-157°C; IR (KBr) 1740, 1720, 1700 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 1.58 (d, J = 11.0 Hz, H17b); 1.78 (d, J = 11.0 Hz, H17a); 2.35 (m, H6,H4); 2.48 (m, H9); 2.58 (m, H7,H5); 2.70 (m, H8); 3.79, 3.81 (s, OCH_3); 3.87 (m, 2H, ethylene acetal); 3.98 (m, 4H, H1,H12, ethylene acetal); 6.36 (m, H15); 6.56 (m, H16); ^{13}C NMR ($CDCl_3$) δ 37.9 (C6); 38.9, 40.0 (C1,C12); 39.7 (C17); 42.0 (C5); 43.1 (C7); 43.7 (C8); 50.9 (C4); 52.3 (2C, OCH_3); 55.5, 58.3 (C2, C11); 53.8 (C9); 65.0, 65.7 (ethylene acetal); 112.9 (C10); 132.6 (C16); 133.1 (C15); 143.2, 143.7 (C13,C14); 166.1, 166.4 (methoxy carbonyl); 212.7 (C3); HRMS requires for $C_{23}H_{22}O_7$ ($M^{+\cdot}$): 410.1365, found: 410.1359. Anal. calcd for $C_{23}H_{22}O_7$: C, 67.31%; H, 5.40%. Found: C, 67.50%; H, 5.40%.

Further elution with a mixture of ether-petroleum ether (7:3) gave 13,14-bis-(methoxycarbonyl)heptacyclo[10.2.2.1^{5,8}.0^{2,6}.0^{2,11}.0^{4,9}.0^{7,11}]heptadeca-13,15-diene-3,10-dione monoethylene acetal **85**, (34 mg) which was recrystallised from a mixture of ether-petroleum ether: mp 172-174°C; IR (KBr) 1740, 1720, 1705 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 1.55 (d, J = 11.0 Hz, H17b); 1.78 (d, J = 11.0 Hz, H17a); 2.18 (m, H6); 2.36 (m, H4); 2.52 (m, H7,H9,H5); 2.72 (m, H8); 3.69, 3.82 (s, OCH_3); 3.84 (m, H12); 3.92 (m, 5H, H1,ethylene acetal); 6.64 (m, H15,H16); ^{13}C NMR ($CDCl_3$) δ 38.2 (C6); 39.2, 40.1 (C1,C12); 39.6 (C17); 42.1 (C5); 43.0 (C7); 44.0 (C8); 50.7 (C4); 51.8, 52.2 (OCH_3); 53.1 (C9); 56.0, 56.1 (C2,C11); 64.9, 66.1 (ethylene acetal); 112.4 (C10); 135.0, 135.2 (C15,C16); 142.5, 143.2 (C13,C14); 166.0, 166.3 (methoxy carbonyl); 212.6 (C3); HRMS requires for $C_{23}H_{22}O_7$ ($M^{+\cdot}$): 410.1365, found: 410.1361. Anal. calcd for $C_{23}H_{22}O_7$: C, 67.31%; H, 5.40%. Found: C, 67.62%; H, 5.11%.

(vi) A solution of **52** (150 mg) and methyl propiolate **73** (96 mg) in toluene (5 mL) was heated under reflux for 31 days. The solvent was removed under reduced pressure to give a residue (425 mg); the ^{1}H NMR and ^{13}C NMR spectra indicated *ca.* 10% unreacted **52** and 4 adducts. The residue was adsorbed onto silica on a radial chromatograph and elution with a mixture of ether and petroleum ether (1:1) gave two fractions which were shown to be mixtures of the adducts. Further elution with ether gave 14-methoxycarbonylheptacyclo[10.2.2.$1^{5,8}$.$0^{2,6}$.$0^{8,11}$.$0^{4,9}$.$0^{7,11}$]heptadeca-13,15-diene-3,10-dione monoethylene acetal **90**, ^{1}H NMR ($CDCl_3$) δ 1.55 (d, J = 10.9 Hz, H17b); 1.77 (d, J = 10.9 Hz, H17a); 2.17, 2.45 (m, H6,H7); 2.34, 2.59 (H4,H9); 2.59, 2.69 (H5,H8); 3.72 - 3.98 (5H, ethylene acetal, H1(H12)); 3.78 (s, CH_3); 4.14 (m, H12(H1)); 6.55, 6.63 (m, H15,H16); 7.23 (dd, J = 6.4 Hz, 1.7 Hz, H13); ^{13}C NMR ($CDCl_3$) δ 36.6, 38.9 (C1,C12); 38.0 (C6); 39.8 (C17); 42.0, 43.0, 43.9, 51.0, 53.6 (C7,C5,C8,C4,C9); 51.6 (CH_3); 65.1, 65.8 (ethylene acetal); 112.9 (C10); 134.1, 135.9 (C15,C16); 145.3 (C13).

The mixtures of adducts from the initial radial chromatographic separation were injected onto a hplc column using Econosil CN (silica-bonded cyanopropyl type) stationary phase, and elution with a 4:1 mixture of dichloromethane and hexane gave 13-methoxycarbonylheptacyclo[10.2.2.$1^{5,8}$.$0^{2,6}$.$0^{2,11}$.$0^{4,9}$.$0^{7,11}$]heptadeca-13,15-diene-3,10-dione monoethylene acetal **89**, ^{1}H NMR ($CDCl_3$) δ 1.56 (d, J = 11.0 Hz, H17b); 1.78 (d, J = 10.9 Hz, H17a); 2.18 (m, H6); 2.33 (m, H4); 2.47 (m, H7,H9); 2.58 (m, H5); 2.71 (m, H8); 3.67 (s, CH_3); 3.74, 3.92, 4.06 (m, ethylene acetal); 3.74 (m, H1); 4.21 (m, H12); 6.48 (m, H15); 6.62 (m, H16); 7.48 (dd, J = 6.5 Hz, 1.7 Hz, H14); ^{13}C NMR ($CDCl_3$) δ 37.6, 37.8 (C1,C12); 38.2 (C6); 39.8 (C17); 42.2 (C5); 43.0 (C7); 44.0 (C8); 50.8 (C4); 51.3 (CH_3); 53.4 (C9); 59.8 (C11); 64.6, 66.0 (ethylene acetal); 112.7 (C10); 134.2 (C15); 136.1 (C16); 138.8 (C13); 144.8 (C14); 214.2 (C3).

Further elution gave 13-methoxycarbonylheptacyclo-[10.2.2.$1^{5,8}$.$0^{2,6}$.$0^{2,11}$.$0^{4,9}$-.$0^{7,11}$]heptadeca-13,15-diene-3,10-dione monoethylene acetal **92**; ^{1}H NMR ($CDCl_3$) δ 1.53 (d, J = 10.9 Hz, H17b); 1.77 (d, J = 10.9 Hz, H17a); 2.13 (m, H6); 2.30 (m, H7);

2.36 (m, H4); 2.46 (m, H9); 2.57 (m, H5); 2.69 (m, H8); 3.78 (s, CH_3); 3.7 - 4.0 (m, 5H, ethylene acetal, H1); 4.19 (m, H12); 6.34 (m, H16); 6.47 (m, H15); 7.51 (dd, J = 6.4 Hz, 1.9 Hz, H14); ^{13}C NMR ($CDCl_3$) δ 37.6 (C1); 38.2 (C6); 38.3 (C12); 39.8 (C17); 42.1 (C5); 43.1 (C7); 43.6 (C8); 50.7 (C4); 51.8 (CH_3); 54.2 (C9); 65.1, 65.8 (ethylene acetal); 112.9 (C10); 132.1 (C15); 134.1 (C16); 134.2 (C13); 146.8 (C14); 165.3 (methoxy carbonyl). Adduct **91** was characterised by its distinct resonances in a ^1H NMR spectrum of a mixture of adducts **89** and **91**: δ 3.76 (s, CH_3); 6.25 (m, 1H); 6.58 (m, 1H); 7.49 (m, 1H).

(vii) To a stirred ice-cooled solution of **52** (200 mg) in dichloromethane (5 mL) was slowly added dropwise a solution of 4-phenyl-1,2,4-triazoline-3,5-dione **41** (150 mg) in dichloromethane (10 mL) until a faint red coloration persisted. The solution was stirred at room temperature for 3 days. The solvent was removed under reduced pressure to give a solid residue which was adsorbed onto silica on a radial chromatograph. Elution with a mixture of ether and petroleum ether (2:3) gave 15-phenyl-13, 15,17-triazaoctacyclo[10.5.2.$1^{5,8}$.$0^{2,6}$.$0^{2,11}$.$0^{4,9}$.$0^{7,11}$.$0^{13,17}$]eicos-18-ene-3,10,14,16-tetraone-10-ethylene acetal **94** (60 mg) which was recrystallised from methanol: mp 266-267°C dec.; IR (KBr) 1715, 1595, 1495 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.76 (d, J = 11.1 Hz, H20b); 1.94 (d, J = 11.2 Hz, H20a); 2.51 (m, H4); 2.61 (m, H9); 2.77 (m , H5); 2.88 (m, H8); 3.04 (m, H6); 3.25 (m, H7); 3.87 (m, ethylene acetal); 5.05 (m, H1,H12); 6.44 (m, H18); 6.60 (m, H19); 7.40 (m, 5H, phenyl); ^{13}C NMR ($CDCl_3$) δ 37.6 (C6); 40.0 (C20); 42.2 (C5); 42.9 (C7); 44.1 (C8); 50.9, 51.7 (C1,C12); 51.3 (C4); 52.2, 54.3 (C2,C11); 54.5 (C9); 65.2, 65.9 (ethylene acetal); 111.4 (C10); 125.6, 128.3, 129.1 (phenyl); 128.9 (C19); 129.4 (C18); 156.1, 156.2 (C14,C16); 209.8 (C3); HRMS requires for $C_{25}H_{21}O_5N_3$ ($M^{+\cdot}$): 443.1482, found: 443.1487. Anal. calcd for $C_{25}H_{21}O_5N_3$: C, 67.71%; H, 4.77%; N, 9.48%. Found: C, 67.40%; H, 4.70%; N, 9.62%.

Further elution with a mixture of ether and petroleum ether (4:1) gave 15-phenyl-13,15,17-triazaoctacyclo[10.5.2.$1^{5,8}$.$0^{2,6}$.$0^{2,11}$.$0^{4,9}$.$0^{7,11}$.$0^{13,17}$]eicos-18-ene-3,10,14,16-tetraone-10-ethylene acetal **93** (21 mg) which was recrystallised from ether-

petroleum ether: mp 275-276°C dec; IR (KBr) 1750, 1700, 1600, 1500 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.56 (d, J = 12.8 Hz, H20b); 1.86 (d, J = 11.2 Hz, H20a); 2.37 (m, H6); 2.55 (m, H7); 2.66 (m, H4,H9,H5); 2.79 (m, H8); 3.98, 4.16 (m, ethylene acetal); 5.11, 5.17 (m, H1,H12); 6.66 (m, H19,H18); 7.39 (m, 5H, phenyl); ^{13}C NMR ($CDCl_3$) δ 38.1 (C6); 38.9 (C20); 41.9 (C5); 42.7 (C7); 43.5 (C8); 49.5, 50.5, 51.5 (C4,C1,C12); 55.1 (C9); 66.1, 66.7 (ethylene acetal); 112.8 (C10); 125.5, 128.1, 129.0, 129.9, 130.2, 130.4 (C18,C19,phenyl); 155.7 (C14,C16); HRMS requires for $C_{25}H_{21}O_5N_3$ (M^+): 443.1482, found: 443.1476. Anal. calcd for $C_{25}H_{21}O_5N_3.H_2O$: C, 65.07%; H, 5.02%; N, 9.11%. Found: C, 65.18%; H, 4.72%; N, 9.15%.

(viii) A solution of **52** (134 mg) and nitrosobenzene **74** (60 mg) in benzene (10 mL) was stirred at room temperature for 2 days. The solvent was removed under reduced pressure to give a solid residue (209 mg). ^1H NMR analysis of the crude reaction mixture indicates a 9:1 ratio of "top face" and "bottom face" isomers. The residue was adsorbed onto silica on a radial chromatograph. Elution with ether-petroleum ether (2:3) gave a mixture of **99** and **100** in a ratio of 2.5:1 (184 mg). Adducts **99** and **100** were confirmed to be both "top face" isomers by NOED spectroscopy on the mixture. The mixture was recrystallised from ethanol to give 14-phenyl-14-aza-13-oxaheptacyclo[$10.2.2.1^{5,8}.0^{2,6}.0^{2,11}.0^{4,9}.0^{7,11}$]heptadeca-15-ene-3,10-dione monoethylene acetal **99**: mp 131-132°C; IR (KBr) 1720, 1590, 1480 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.76 (d, J = 10.9 Hz, H17b); 1.91 (d, J = 11.0 Hz, H17a); 2.47 (m, H4); 2.57 (m, H9); 2.76 (m, H5); 2.86 (m, H8); 3.23 (m, H6); 3.29 (m, H7); 3.85 (m, 4H, ethylene acetal); 4.58 (d, $J_{H1,H16}$ = 5.8 Hz, H1); 4.70 (d, $J_{H12,H15}$ = 6.0 Hz, H12); 6.24 (m, H16); 6.51 (m, H15); 6.95, 7.21 (m, 5H, phenyl); ^{13}C NMR ($CDCl_3$) δ 37.2 (C6); 40.1 (C17); 42.3 (C5); 42.4 (C7); 43.7 (C8); 51.0, 54.8 (C2,C11); 51.5 (C4); 54.9 (C1); 65.0, 65.8 (ethylene acetal); 70.0 (C12); 111.8 (C10); 117.3, 122.1, 128.4, 151.9 (phenyl); 129.1 (C16); 129.5 (C15); 212.1 (C3); HRMS requires for $C_{23}H_{21}NO_4$ ($M^{+\cdot}$): 375.1471, found: 375.1469. Anal. calcd for $C_{23}H_{21}NO_4$: C, 73.58%; H, 5.64%; N, 3.73%. Found: C, 73.72%; H, 5.55%; N, 3.64%. Adduct **100** was

characteristed by the following distinct signals in the ^{1}H NMR ($CDCl_3$) of a mixture of **99** and **100**: δ 4.47 (dd, 1H); 4.73 (dd, 1H); 6.50 (m, 1H); 6.70 (m, 1H).

2.2 Diels-Alder reactions of the monoethylene thioacetal diene 53

(i) A solution of **53** (150 mg) and maleic anhydride **38** (64 mg) in benzene (7 mL) was heated under reflux for 3 days. The product 15-oxaoctacyclo-[10.5.2.1^{5,8}.0^{2,6}.0^{2,11}.0^{4,9}.0^{7,11}.0^{13,17}]eicos-18-ene-3,10,14,16-tetraone-10-ethylene thioacetal **76** crystallised from the reaction mixture (89 mg): mp 287-288°C; IR (KBr) 1865, 1775, 1730 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 1.49 (d, J = 11.3 Hz, H20b); 1.86 (d, J = 11.2 Hz, H20a); 2.20 (m, H6); 2.58 (m, H4,H5,H7); 2.80 (m, H8); 3.08 (m, H9); 3.36 (m, 5H, H1,ethylene thioacetal); 3.67 (m, H12,H17); 4.20 (dd, $J_{H13,H17}$ = 8.9 Hz, $J_{H13,H12}$ = 3.5 Hz, H13); 6.53 (m, H18,H19); ^{13}C NMR δ 32.3 (C1); 36.0 (C12); 38.3 (C20); 38.6, 41.4 (ethylene thioacetal); 38.9 (C6); 40.4 (C17); 41.4 (C13); 42.3 (C5); 46.4 (C8); 46.9 (C7); 52.4, 56.9 (C2,C11); 53.7 (C4); 66.1 (C9); 75.0 (C10); 133.0, 134.9 (C18,C19); 172.3, 172.9 (C14,C16); 214.0 (C3); HRMS requires for $C_{21}H_{18}S_2O_4$ ($M^{+\cdot}$): 398.0646, found: 398.0647. Anal. calcd for $C_{21}H_{18}S_2O_4$: C, 63.29%; H, 4.55%. Found: C, 63.30%; H, 4.41%.

(ii) A solution of **53** (300 mg) and methyl vinyl ketone **72** (2 mL) was heated under reflux in toluene (15 mL) for 51 days. The solvent was removed under reduced pressure to give a residue (900 mg); ^{1}H NMR analysis of the residue indicated *ca.* 50% unreacted **53** and a mixture of two adducts. The residue was adsorbed onto silica on a radial chromatograph and elution with ether-petroleum ether (1:4) gave unreacted monothioacetal **53** (142 mg). Further elution gave 14-acetylheptacyclo-[10.2.2.1^{5,8}.0^{2,6}.0^{2,11}.0^{4,9}.0^{7,11}]heptadeca-15-ene-3,10-dione mono-ethylene thioacetal **83** (36 mg) which was recrystallised from methanol: mp 161-162°C; IR (KBr) 1719, 1695 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 1.34 (m, H13b); 1.42 (d, J = 11.0 Hz, H17b); 1.79 (d, J = 10.9 Hz, H17a); 2.13 (m, H6(H7)); 2.16 (s, CH_3); 2.47 (m, 4H, H4(H9); H5(H8); H7(H6); H13a); 2.72 (m, H8(H5)); 3.02 (m, 3H, H1,H12,H9(H4)); 3.29 (m, 5H, ethylene thioacetal, H14); 6.27 (m, H16); 6.51 (m, H15); ^{13}C NMR ($CDCl_3$) δ

24.3 (C13); 28.5 (CH_3); 31.8 (C12); 35.2 (C1); 38.4 (C17, ethylene thioacetal); 38.9, 47.4 (C6,C7); 41.3 (C2,C11); 42.4, 66.1 (C4,C9); 45.8 (C14); 46.4, 54.0 (C5,C8); 76.9 (C10); 131.3 (C16); 136.6 (C15); 209.7 (acetyl carbonyl); 213.4 (C3); HRMS requires for $C_{21}H_{22}S_2O_2$ ($M^{+\cdot}$): 370.1061, found: 370.1063. Further elution with ether-petroleum ether (1:1) gave a mixture of **83** and **84** and repeated attempts at recrystallisation gave only mixtures of the two compounds. The identity of **84** as the corresponding regioisomer was confirmed by NOED NMR experiments on the mixture. Adduct **84** is characterised by the following distinct ^1H NMR ($CDCl_3$) signals in a spectrum of a mixture of **83** and **84**: δ 6.32 (m, 1H); 6.40 (m, 1H).

(iii) A solution of **53** (200 mg) and dimethylacetylene dicarboxylate **40** (242 mg) was heated under reflux in benzene (10 mL) for 21 days. The solvent was removed under reduced pressure to give a residue which was adsorbed onto silica on a radial chromatograph. Elution with a mixture of ether and petroleum ether (2:3) gave unreacted **53** (137 mg). Further elution with a mixture of ether and petroleum ether (1:1) gave 13,14-bis(methoxycarbonyl)heptacyclo[$10.2.2.1^{5,8}.0^{2,6}.0^{2,11}.0^{4,9}.0^{7,11}$]heptadeca-13,15-diene-3,10-dione monoethylene thioacetal **88** (225mg) which was recrystallised from ethanol: mp 131-132°C; IR (KBr) 2990, 1720, 1650, 1500 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.57 (d, J = 11.1 Hz, H20b); 1.85 (d, J = 11.0 Hz, H20a); 2.27 (m, H6); 2.48 (m, H4); 2.59 (m, H5); 2.66 (m, H7); 2.88 (m, H8); 3.00 (m, H9); 3.22 (m, ethylene thioacetal); 3.80, 3.83 (s, OCH_3); 4.01 (m, H1); 4.38 (m, H12); 6.55 (m, H15,H16); ^{13}C NMR ($CDCl_3$) δ 37.5 (C6); 38.9, 39.7 (ethylene thioacetal); 39.2 (C17,C1); 42.3 (C5); 43.5 (C12); 45.9 (C7); 46.9 (C8); 52.4 (2C, OCH_3); 52.9 (C4); 57.9, 64.2 (C2,C11); 64.0 (C9); 76.3 (C10); 131.7, 135.6 (C15,C16); 143.2, 144.6 (C13,C14); 166.4 (methoxy carbonyl); 213.9 (C3); HRMS requires for $C_{23}H_{22}S_2O_5$ ($M^{+\cdot}$): 442.0907, found: 442.0903. Anal. calcd for $C_{23}H_{22}S_2O_5$: C, 62.42%; H, 5.01%. Found: C, 62.33%; H, 5.11%.

(iv) To a stirred ice-cooled solution of **53** (168 mg) in dichloromethane (10 mL) was slowly added portionwise 4-phenyl-1,2,4-triazoline-3,5-dione **41** (140 mg) until a faint red coloration persisted. The solution was stirred at 0-5°C for a further 90 minutes.

The solvent was removed under reduced pressure to give a solid residue which was adsorbed onto silica on a radial chromatograph. Elution with a mixture of ether and petroleum ether (1:1) gave 15-phenyl-13,15,17-triazaoctacyclo[10.5.2.$1^{5,8}$.$0^{2,6}$.-$0^{2,11}$.$0^{4,9}$.$0^{7,11}$.$0^{13,17}$]eicos-18-ene-3,10,14,16-tetraone-10-ethylene thioacetal **96** (330 mg) which was recrystallised from ethanol: mp 236-237°C; IR (KBr) 3100, 2950, 1720, 1600, 1500 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.76 (d, J = 11.2 Hz, H20b); 2.01 (d, J = 11.3 Hz, H20a); 2.61 (m, H4); 2.72 (m, H5); 3.01 (m, H6,H8); 3.12 (m, H9); 3.19 (m, 3H, ethylene thioacetal); 3.33 (m, 2H, ethylene thioacetal, H7); 5.05 (m, H1); 5,33 (m, H12); 6.57 (m, H18,H19); 7.37, 7.46 (phenyl); ^{13}C NMR ($CDCl_3$) δ 36.8 (C6); 39.2, 40.0 (ethylene thioacetal); 39.5 (C20); 42.4 (C5); 45.5 (C7); 47.1 (C8); 50.8 (C1); 53.3 (C4); 54.7 (C2); 54.8, 60.0 (C2,C11); 64.6 (C9); 73.6 (C10); 125.5, 128.3, 129.1 (phenyl); 127.5, 131.2 (C18,C19); 156.0, 156.1 (C14,C16); HRMS requires for $C_{25}H_{21}S_2N_3O_3$ ($M^{+\cdot}$): 475.1024, found: 475.1016. Anal. calcd for $C_{25}H_{21}S_2N_3O_3$: C, 63.14%; H, 4.45%; N, 8.84%. Found: C, 63.25%; H, 4.35%; N, 9.05%.

(v) A solution of **53** (300 mg) and nitrosobenzene **74** (188 mg) was heated under reflux in benzene (25 mL) for 9 days. The solvent was removed under reduced pressure to give a residue (478 mg), the ^1H NMR of which indicated *ca.* 10% unreacted **53** and the formation of two adducts in a ratio of 7:3. The residue was adsorbed onto silica on a radial chromatograph and careful elution with petroleum ether gave fractions which were mixtures of the two adducts **101** and **102**. Repeated chromatographic separation and recrystallisation failed to give pure samples of the adducts. The stereochemistries of **101** and **102** was deduced from NOED NMR experments performed on the mixture. **101** and **102** are characterised by the following NMR data ($CDCL_3$) : δ for **101** (**102**) 4.62 (dd, 1H); 4.98 (dd, 1H); 6.21 (m, 1H); 6.63 (m, 1H); δ for **102** (**101**) 4.75 (dd, 1H); 4.80 (dd, 1H); 6.30 (m, 1H); 6.67 (m, 1H).

3.1.1 Synthesis of cage dialkane 103

(i) by reduction of diketone **35** with hydrazine hydrate in potassium hydroxide and diethylene glycol.

A mixture of diketone **35** (500 mg, 2.23 mmole) and hydrazine monohydrate (670 mg, 13.4 mmole) was stirred in diethylene glycol (20 mL) at *ca.* 120°C for 2.5 hours. After addition of potassium hydroxide (500 mg), the reaction mixture was heated to 190°C and maintained at this temperature for a further 21 hours. The reaction mixture was extracted with dichloromethane (3 x 30 mL). The extracts were washed with water (2 x 10 mL) and dried over magnesium sulphate. The solvent was removed under reduced pressure to give a residue (454 mg). A portion of the residue (30 mg) was adsorbed onto a silica column and elution with petroleum ether gave hexacyclo[10.2.1.$0^{2,11}$.$0^{4,9}$.$0^{4,14}$.$0^{9,13}$]pentadeca-5,7-diene **103** (10 mg) as an oil. ^{1}H NMR ($CDCl_3$) δ 0.91 (d, J = 12.0 Hz, 2H, *endo* -H3,H10); 1.02 (d, J = 10.5 Hz, H15b); 1.52 (d, J = 10.2 Hz, H15a); 1.72 (d, J = 12.1 Hz, *exo* -H3,H10); 2.28, 2.35, 2.76 (m, 6H, H1,H2,H11,H12,H13,H14); 5.33 (m, H5,H8); 5.66 (m, H6,H7); ^{13}C NMR ($CDCl_3$) δ 31.4 (C15); 33.8 (C3,C10); 46.0 (C4,C9); 42.7, 47.2, 57.1 (C1,C2,C11,C12,C13,C14); 121.1 (C5,C8); 130.0 (C6,C7); HRMS requires for $C_{15}H_{16}$ ($M^{+\cdot}$): 196.1252, found: 196.1256.

(ii) by reduction of diketone **35** with hydrazine hydrate in potassium t-butoxide and toluene.

A mixture of the cage diketone **35** (500 mg, 2.23 mmole) and hydrazine monohydrate (670 mg, 1.34 mmole) was heated under reflux in toluene (40 mL) for 2 hours. Removal of the solvent under reduced pressure gave a residue (647 mg); ^{1}H NMR of the residue indicated two cage products, a symmetrical and unsymmetrical compound, possibly the mono- and di-hydrazones. A mixture of the crude hydrazone product(s) (200 mg) and potassium t-butoxide (500 mg) in toluene (20 mL) was heated under reflux for 22 hours. The reaction mixture was washed with water (2 x 15 mL) and the water layer was re-extracted with ether (3 x 30 mL). The combined toluene and ether extracts were dried over sodium sulphate. Removal of the solvent gave a crude residue

(62 mg), the ^{1}H NMR spectral analysis of which indicated an intractable mixture. However none of the signals expected for the dialkane **103** was observed in this spectrum.

(iii) by reduction of the diketone **35** with hydrazine hydrate in potassium t-butoxide in dimethyl sulphoxide at room temperature.

A mixture of cage diketone **35** (300 mg) and hydrazine hydrate (1 mL) in toluene (10 mL) was heated under reflux for 2 hours. A white solid precipitated out of the reaction mixture. The solid was filtered, washed with toluene (5 mL) and dried in vacuo overnight over phosphorus pentoxide. ^{1}H NMR analysis of this solid (**a**) (101 mg) indicated a mixture of a symmetrical and an unsymmetrical cage diene in a ratio of 3:7. IR (KBr) 3280, 3220 cm^{-1}. MS analysis showed molecular ion peaks at 270, 271, 311, 343, 373, 407 and 539 a.m.u. The filtrate was extracted with dichloromethane (30 mL), washed with water (20 mL) and dried over sodium sulphate. Removal of the solvent gave a yellowish residue (**b**) (143 mg); ^{1}H NMR spectral analysis of the residue suggested a major diene product and polymeric material. The IR spectrum of the residue showed clearly the absence of a carbonyl absorption.

The residue (**a**) (50 mg) and potassium t-butoxide (100 mg) were stirred in dry dimethyl sulphoxide (2 mL) at room temperature for 12 hours. Ether (35 mL) and water (5 mL) were added to the reaction mixture. The ether layer was separated and washed with dilute hydrochloric acid (1N, 10 mL), saturated sodium chloride solution (10 mL) and dried over sodium sulphate. Removal of the solvent gave a crude product, the ^{1}H NMR of which indicated polymeric material.

A mixture of the residue (**b**) (101 mg) and potassium t-butoxide (207 mg) was stirred in dry dimethyl sulphoxide (2 mL) at room temperature for 12 hours. The reaction mixture was worked up in the same manner as the reaction of residue (**a**). Removal of the solvent gave a crude product (15 mg), the ^{1}H NMR of which indicated the presence of the dialkane **103**.

3.1.2 Attempted syntheses of monoalkane 105

(i) by Wolff-Kishner reaction of monoethylene acetal **52**

A mixture of the monoethylene acetal **52** (100 mg) and hydrazine hydrate (0.1 mL) was heated under reflux in ethanol (10 mL) for 4.5 hours. Removal of the solvent gave a residue (104 mg), the ^{1}H NMR analysis of which showed an intractable mixture. A mixture of this residue (104 mg) and potassium t-butoxide (200 mg) was stirred in dry dimethyl sulphoxide (2 mL) for 12 hours. Ether (35 mL) and water (5 mL) were added to the reaction mixture. The ether layer was separated, washed with dilute hydrochloric acid (1N, 10 mL) and dried over sodium sulphate. Removal of the solvent gave a residue which was hydrolysed in a mixture of aqueous hydrochloric acid (6% v/v, 10 mL) and tetrahydrofuran (3 mL) at 60°C for 2 hours. The reaction mixture was cooled and extracted with dichloromethane (2 x 20 mL), washed with sodium bicarbonate solution (10% w/v, 10 mL), water (2 x 10 mL) and dried over sodium sulphate. Removal of the solvent gave a residue and examination of its ^{1}H NMR spectrum indicated a very complex mixture.

(ii) by Clemmensen reduction of the cyclopentadiene-1,4-naphthoquinone adduct **44**

A mixture of zinc dust (196 mg) and mercuric chloride (20 mg) was stirred in conc. hydrochloric acid (1 mL) and water (25 mL) for 5 mins. The aqueous layer was decanted leaving an amalgam of zinc/mercury. A mixture of the amalgam and the Diels-Alder adduct **44** (224 mg, 1 mmole) in conc. hydrochloric acid (25 mL) was heated under reflux for 5 hours. Monitoring by t.l.c. analysis on silica (chloroform, as elutant) indicated the absence of starting materials. The reaction mixture was cooled and extracted with dichloromethane (2 x 25 mL), washed with sodium hydroxide solution (10% w/v, 2 x 20 mL), water (2 x 20 mL) and dried over sodium sulphate. Removal of the solvent gave a residue, the ^{1}H NMR of which indicated a mixture of decomposition products with the olefinic protons clearly absent.

(iii) by the reduction of the tosylhydrazone **107** of cyclopentadiene-1,4-naphthoquinone adduct.

*(a) Synthesis of tosylhydrazone **107**.* p-Toluenesulphonyl hydrazine (262 mg, 1.41 mmole) was added portionwise to a stirred solution of the cyclopentadiene-1,4-naphthoquinone adduct **44** (300 mg, 1.34 mmole) in glacial acetic acid (5 mL). When the addition was completed, the reaction mixture was stirred overnight at room temperature. Removal of the solvent in vacuo overnight gave a residue (599 mg); ^{1}H NMR of the residue indicated a mixture of ditosylhydrazone of **44**, monotosylhydrazone **107** and unreacted cyclopentadiene-1,4-naphthoquinone adduct **44** in a ratio of 1:1.6:1.7. The residue was adsorbed onto silica on a radial chromatograph and elution with a mixture of ether-petroleum ether (1:1) gave unreacted cyclopentadiene-1,4-naphthoquinone adduct **44** (197 mg). Further elution gave the monotosylhydrazone **107** (143 mg); ^{1}H NMR (DMSO) δ 1.45 (d, J = 8.6 Hz, H15b); 1.54 (d, J = 8.5 Hz, H15a); 2.45 (s, CH_3); 3.38, 3.83 (m, H2,H11); 3.45, 3.72 (br s, H1,H12); 5.77, 5.85 (m, H13,H14); 7.50, 7.91 (d, J = 8.1 Hz, J = 8.3 Hz, 4H, -SO_2-$C_6\underline{H}_4$-CH_3); 7.55, 7.68 (m, H5,H8); 7.82, 7.97 (d, J = 7.8 Hz, J = 8.0 Hz, H6,H7); ^{13}C NMR (DMSO) δ 21.1 (CH_3); 37.7 (C15); 45.9, 48.0, 48.9, 49.8 (C1,C2,C11,C12); 124.2, 125.9, 127.5, 128.3, 129.7 (2C), 132.1, 134.0, 134.4, 135.5 (-SO_2-$\underline{C}_6H_4$-CH_3,C5,C6,C7,C8); 197.8 (C3).

Further elution gave the ditosylhydrazone of **44** (136 mg); ^{1}H NMR (DMSO) δ 1.43 (d, J = 8.1 Hz, H15b); 1.48 (d, J = 8.0 Hz, H15a); 2.43 (s, 6H, 2 x CH_3); 3.54 (br s, H1,H12); 3.75 (br s, H2,H11); 5.58 (s, H13,H14); 7.38 (m, H5,H8); 7.46, 7.86 (d, J = 8.4 Hz, 8.0 Hz, 8H, 2 x -SO_2-$C_6\underline{H}_4$-CH_3); 7.71 (m, H6,H7); 10.89 (s, 2 x NH).

*(b) reduction of monotosylhydrazone **107**.* Sodium borohydride (170 mg, 4.59 mmole) was added portionwise to a cooled solution of the monotosylhydrazone **107** (181 mg, 0.46 mmole) in dry methanol (10 mL). When the addition was completed, the reaction mixture was heated under reflux for 13 hours. The reaction mixture was cooled

and the solvent was removed under reduced pressure to give a residue. The residue was dissolved in water (20 mL) and extracted with ether (10% w/v), 2 x 25 mL), washed with water (20 mL) and dried over sodium sulphate. Removal of the solvent gave a crude product mixture (80 mg), the ^{1}H NMR of which showed a complex mixture. Attempted chromatographic separation of the product mixture did not yield any identifiable product.

(iv) by desulphurisation of the monothioacetal **53**

(a) with Raney-nickel catalyst in ethanol. Raney-nickel catalyst (W2 grade) was freshly prepared.[99b] A mixture of the monothioacetal **53** (79 mg) and Raney-nickel catalyst (1 g) was heated under reflux in ethanol (25 mL) for 45 hours. The reaction mixture was filtered through Celite and the Celite was washed with ethanol (10 mL). Removal of the solvent from the filtrate gave a residue, the ^{1}H NMR spectrum of which indicated an intractable mixture. However the thioacetal moiety was clearly absent but the diene moiety had also been reduced. The reaction was also unsuccessful when repeated at room temperature for a week was also unsuccessful.

An attempt at moderation of the activity of the Raney-nickel catalyst by inclusion of 2% acetic acid in the reaction mixture resulted in the inactivation of the catalyst and the thioacetal **53** was recovered unreacted.

(b) with a mixture of cupric chloride, zinc chloride and lithium aluminium hydride. A mixture of anhydrous cupric chloride (179 mg, 1.33 mmole), zinc chloride (182 mg, 1.33 mmole) and lithium aluminium hydride (202 mg, 5.33 mmole) was stirred in dry tetrahydrofuran (20 mL) under a dry nitrogen atmosphere. Monothioacetal **53** (100 mg, 0.33 mmole) was added to the above mixture and the reaction mixture was heated under reflux for 10 hours. The reaction mixture was cooled and the excess reducing agent was destroyed by careful addition of water (20 mL). It was extracted with ether (2 x 20 mL) and the combined extracts were dried over calcium sulphate. Removal of the solvent gave a residue, the ^{1}H NMR analysis of which revealed unreacted monothioacetal **53**.

(c) with hydrazine hydrate in diethylene glycol. A mixture of the monothioacetal **53** (69 mg), hydrazine hydrate (0.35 mL) and potassium hydroxide (140 mg) in diethylene glycol (5 mL) was heated at *ca.* 135 -155°C for 5 hours. The reaction mixture was cooled and extracted with dichloromethane (3 x 10 mL), washed with water (2 x 10 mL) and dried over sodium sulphate. Removal of the solvent gave a residue (61 mg), the ^{1}H NMR analysis of which showed a complex mixture of products.

(v) via reduction of monotosylhydrazone **106** (see later).

3.1.3 Synthesis of dioxime 104

A solution of cage diketone **35** (0.56 g, 2.5 mmole), hydroxylamine hydrochloride (0.70g, 10.0 mmole) and potassium carbonate (0.69 g, 5.0 mmole) in a 2:1 mixture of ethanol and water (30 mL) was heated under reflux for 5 hours. The reaction mixture was reduced in volume to *ca.* 15 mL and water (10 mL) was added. The product precipitated out of the reaction mixture and was filtered and washed with water (2 mL). Aqueous hydrochloric acid (5% v/v, 15 mL) was added to the filtrate and a second crop of product was obtained and treated in the same manner. The product **104** was dried in vacuo over silica gel for a day (494 mg, 72%): mp 238-240°C; IR (KBr) 3300, 1670 cm^{-1}. ^{1}H NMR ($CDCl_3$ - CF_3COOH) δ 1.60 (d, J = 11.6 Hz, H15b); 1.98 (d, J = 11.6 Hz, H15a); 2.91 (m, H1,H12); 3.22 (m, H13,H14); 3.95 (m, H2,H11); 5.48 (m, H5,H8); 6.05 (m, H6,H7); ^{13}C NMR ($CDCl_3$ - CF_3COOH) δ 37.1 (C15); 44.7 (C2,C11); 46.2 (C1,C12); 49.8 (C4,C9); 54.0 (C13,C14); 119.2 (C5,C8); 125.3 (C6,C7); 166.1 (C3,C10); HRMS requires for $C_{15}H_{14}N_2O_2$ ($M^{+\cdot}$): 254.1055, found: 254.1057. Anal. calcd for $C_{15}N_{14}N_2O_2$: C, 70.85%; H, 5.55%; N, 11.02%. Found: C, 70.56%; H, 5.21%; N, 11.15%.

Reduction of the dioxime 104

To an ice-cooled, stirred suspension of the dioxime **104** (200 mg, 0.79 mmole) in dry tetrahydrofuran (5 mL) was added lithium aluminium hydride (162 mg, 4.27 mmole) in dry tetrahydrofuran (5 mL). The reaction mixture was allowed to warm to room temperature and stirred for an hour and subsequently was heated under reflux for 2

hours. The cooled reaction mixture was treated with water and extracted with benzene (4 x 20 mL). The combined extracts were dried over potassium hydroxide and the solvent was removed to give a residue (76 mg). ^{1}H NMR analysis of the residue indicated an intractable mixture of products.

Attempted condensation reactions of nitrogen nucleophiles with the cage diketone 35

(i) with benzylamine

A mixture of the cage diketone **35** (50 mg, 0.22 mmole) and benzylamine (25 mg, 0.23 mmole) was stirred in tetrahydrofuran (1 mL) at 0-5°C for 5 hours. Monitoring of the reaction by t.l.c. indicated that the reaction was completed after 5 hours. Removal of the solvent gave a residue (24 mg); examination of the ^{1}H NMR spectrum of the residue revealed a very complex mixture.

(ii) with o-phenylenediamine

A mixture of the cage diketone **35** (112 mg, 0.5 mmole) and o-phenylenediamine (54 mg, 0.5 mmole) was stirred at room temperature for 1 day. Removal of the solvent gave a residue, the ^{1}H NMR anaylsis of which indicated unreacted diketone **35**. The reaction was repeated at 80°C for 3 hours. Removal of the solvent gave a residue; ^{1}H NMR of the residue indicated decomposition of the starting materials.

(iii) with aniline

A mixture of cage diketone **35** (112 mg, 0.5 mmole) and aniline (93 mg, 1 mmole) was stirred in benzene (10 mL) at room temperature for 1 day. Removal of the solvent gave a residue (235 mg) which was analysed by ^{1}H NMR to be a complex mixture. However the diene moiety was clearly absent, instead peaks in the aromatic region were present, indicative of the occurence of rearrangement reaction(s) leading to the formation of these aromatic product(s). The residue was adsorbed onto silica on a radial chromatograph and elution with mixtures of petroleum ether and ether gave mixtures of unidentifiable product(s). Further elution with ether gave an aromatic product (24 mg) which was not identified. ^{1}H NMR (CD_3OD) δ 1.62, 2.30 (d, 2H);

2.98 (d, 1H), 3.08 (d, 1H); 3.27 (m, 1H); 3.28 (d, 1H); 3.64 (m, 1H); 3.82 (s, 1H); 6.80 - 7.63 (m, 9H).

(iv) with 1,2-diaminoethane

A mixture of the cage diketone **35** (200 mg, 0.89 mmole) and 1,2-diaminoethane (107 mg, 1.78 mmole) was stirred in dichloromethane (20 mL) at 0-5°C for 2 days. The solvent was removed to give a residue (240 mg); ^{1}H NMR analysis of the residue in d_6-DMSO revealed the presence of two cage diene products as seen from the two AB-quartet between 1.3 - 1.8 ppm and the diene moieties between 5.4 - 6.0 ppm. An infrared spectrum of the residue showed OH and NH absorptions at *ca.* 3400 cm^{-1} but clearly a carbonyl absorption was absent. HRMS analysis of the residue gave a molecular ion peak at 266.1411 (monoimine **111** $C_{17}H_{18}N_2O$ ($M^{+\cdot}$) requires 266.1419). Therefore the evidence suggests that the major product was the monoimine **111**. However attempted dehydration of the residue to the diimine **112** by heating under reflux in benzene, catalysed by p-toluenesulphonic acid was unsuccessful.

3.2 Diels-Alder reactions of dialkane 103 and dioxime 104

Diels-Alder reactions of the dialkane 103

The crude product from the preparation of the dialkane **103** was used without purification in the subsequent Diels-Alder reactions.

(i) A solution of **103** (193 mg) and maleic anhydride **38** (98 mg) in benzene (10 mL) was heated under reflux for 4 days. The solvent was removed under reduced pressure to give a residue, the ^{1}H NMR of which indicated the formation of a single adduct. The residue was adsorbed onto silica on a radial chromatograph and elution with a mixture of ether and petroleum ether 1:1 gave 15-oxaoctacyclo[10.5.2,1^{5,8}.0^{2,6}.0^{2,11}-.0^{4,9}.0^{7,11}.0^{13,17}]eicos-18-ene-14,16-dione **113** (49 mg) which was recrystallised from a mixture of ether and petroleum ether: mp 180-181°C; IR (KBr) 1800, 1760 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 1.09 (d, J = 11.9 Hz, *endo* -H3,H10); 1.12 (d, J = 10.5 Hz, H20b); 1.34 (d, J = 12.00 Hz, *exo* -H3,H10); 1.57 (d, J = 10.3 Hz, H20a); 2.02 (br s, H6,H7); 2.30 (m, H4,H9,H5,H8); 3.02 (m, H1,H12); 3.13 (m, H13,H17); 6.44

(m, H18,H19); ^{13}C NMR ($CDCl_3$) δ 29.7 (C10); 34.5 (C20); 38.4 (C1,C12); 41.4 (C5,C8); 42.2 (C13,C17); 45.2 (C6,C7); 46.1 (C4,C9); 48.9 (C2,C11); 133.2 (C18,C19); 173.2 (C14,C16); HRMS requires for $C_{19}H_{18}O_3$ ($M^{+\cdot}$): 294.1257, found: 294.1259. Anal. calcd for $C_{19}H_{18}O_3$: C, 77.53%; H, 6.16%. Found: C, 77.29%; H, 6.29%.

(ii) A solution of **103** (79 mg) and dimethylacetylene dicarboxylate **40** (57 mg) in benzene (10 mL) was heated under reflux for 11 days. The solvent was removed under reduced pressure to give an oil; ^1H NMR analysis of this sample indicated the reaction was completed and only one adduct was formed. The oil was adsorbed onto silica on a radial chromatograph and elution with a mixture of ether and petroleum ether (1:4) gave a fraction containing the adduct and unreacted dimethyacetylene dicarboxylate. Recrystallisation of this fraction from ether and petroleum ether gave 13,14-bis-(methoxycarbonyl)heptacyclo[10.2.2.$1^{5,8}$.$0^{2,6}$.$0^{2,11}$.$0^{4,9}$.$0^{7,11}$]heptadeca-13,15-diene **117**: mp 89-90°C; IR (KBr) 1705, 1675 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.13 (s, 4H, H3,H10); 1.19 (d, J = 10.1 Hz, H17b); 1.58 (d, J = 10.5 Hz, H17a); 1.94 (m, H6,H7); 2.19 (br s, $W_{h/2}$ = 4 Hz, H5,H8,H4,H9); 3.77 (m, 8H, H1,H12, OCH_3); 6.52 (m, H15,H16); ^{13}C NMR ($CDCl_3$) δ 31.4 (C3,C10); 36.4 (C17); 41.5 (C5,C8); 43.9 (C6,C7); 45.6 (C1,C12); 45.8 (C4,C9); 52.1 (OCH_3); 52.9 (C2,C11); 133.6 (C15,C16); 141.9 (C13,C14); 166.9 (methoxy carbonyl); HRMS requires for $C_{21}H_{22}O_4$ ($M^{+\cdot}$): 338.1518, found: 338.1517. Anal. calcd for $C_{21}H_{22}O_4$: C, 74.54%; H, 6.55%. Found: C, 74.71%; H, 6.40%.

(iii) To a stirred ice-cooled solution of **103** (44 mg) in dichloromethane (2 mL) was slowly added dropwise a solution of 4-phenyl-1,2,4-triazoline-3,5-dione **41** (39 mg) in dichloromethane (2 mL) until a faint red coloration persisted. The solution was stirred at room temperature for a further 1.5 hours. The solvent was removed under reduced pressure to give a residue (52 mg), the ^1H NMR analysis of which indicated the presence of only one adduct. The residue was adsorbed onto silica on a radial chromatograph and elution with petroleum ether gave 15-phenyl-13,15,17-triazaoctacyclo-[10.5.2.$1^{5,8}$.$0^{2,6}$.$0^{2,11}$.$0^{4,9}$.$0^{7,11}$.$0^{13,17}$]eicos-18-ene-14,16-dione **118** (10 mg) which

was recrystallised from chloroform: mp 221-222°C; IR (KBr) 1770, 1700, 1600, 1500 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.16 (d, J = 10.5 Hz, H20b); 1.28 (d, J = 12.0 Hz, *exo* -H3,H10); 1.63 (d, J = 10.6 Hz, H20a); 1.73 (d, J = 12.2 Hz, *endo* -H3,H10); 2.10 (m, H6,H7); 2.35 (m, H5,H8); 2.39 (m, H4,H9); 4.76 (m, H1,H12); 6.62 (m, H18,H19); 7.35, 7.45 (m, phenyl); ^{13}C NMR ($CDCl_3$) δ 29.8 (C3,C10); 34.4 (C20); 41.6 (C4,C9); 43.4 (C6,C7); 46.5 (C5,C8); 47.5 (C2,C11); 56.1 (C1,C12); 125.6, 128.1, 129.0 (phenyl); 130.2 (C18,C19); 155.7 (C14,C16); HRMS requires for $C_{23}H_{21}N_3O_2$ ($M^{+\cdot}$): 371.1634, found: 371.1642. Anal. calcd for $C_{23}H_{21}N_3O_2$: C,74.37%; H, 5.70%; N, 11.31%. Found: C, 73.93%; H, 5.64%; N, 11.44%.

3.2 Diels-Alder reactions of the dioxime 104

(i) A solution of dioxime **104** (150 mg) and maleic anhydride **38** (58 mg) in benzene (10 mL) was heated under reflux for 16 hours. ^1H NMR of the reaction mixtrue shown the presence of a single adduct. The solvent was removed under reduced pressure to give 15-oxaoctacyclo[$10.5.2.1^{5,8}.0^{2,6}.0^{2,11}.0^{4,9}.0^{7,11}.0^{13,17}$]eicos-3,10,14,16-tetraone-3,10-dioxime **114** (208 mg) which was washed with acetonitrile, dried in vacuo: mp 307-308°C dec.; IR (KBr) 3540, 3315, 1860, 1770, 1680 cm^{-1}. ^1H NMR (DMSO) δ 1.51 (d, J = 10.7 Hz, H20b); 1.86 (d, J = 10.6 Hz, H20a); 2.43 (m, H6,H7); 2.59 (m, H5,H8); 3.32 (m, H1,H12); 3.68 (m, H4,H9); 3.92 (s, H13,H17); 6.58 (m, H18,H19); 10.77 (s, H3,H10); ^{13}C NMR (DMSO) δ 33.3 (C1,C12); 38.0 (C20); 41.0 (C13,C17); 42.9 (C4,C9); 43.7 (C6,C7); 44.5 (C5,C8); 51.4 (C2,C11); 133.2 (C18,C19); 160.6 (C3,C10); 174.0 (C14,C16); HRMS requires for $C_{19}H_{16}N_2O_5$ ($M^{+\cdot}$): 352.1059, found: 352.1058. Anal. calcd for $C_{19}H_{16}N_2O_5$: C, 64.77%; H, 4.58%; N, 7.95%. Found: C, 64.64%; H, 4.77%; N, 8.01%.

(ii) A solution of dioxime **104** (100 mg) and benzoquinone **39** (43 mg) in benzene (25 mL) was heated under reflux for 1 day. The solvent was removed under reduced pressure to give a solid, the ^1H NMR analysis of which indicated the presence of *ca.* 60% unreacted dioxime and a single adduct. The crude product was washed with acetone to remove **115** which was dried in vacuo overnight. The product

octacyclo[10.6.2.$1^{5,8}$.$0^{2,6}$.$0^{2,11}$.$0^{4,9}$.$0^{7,11}$.$0^{13,18}$]heneicosa-15,19-diene-3,10,14,17-tetraone-3,10-dioxime **115** (44 mg) was obtained: mp > 360°C dec.; IR (KBr) 3300, 1660 cm^{-1}. ^1H NMR (DMSO) δ 1.48 (d, J = 11.0 Hz, H21b); 1.84 (d, J = 10.3 Hz, H21a); 2.39 (br s, $W_{h/2}$ = 7 Hz, H6,H7); 2.57 (m, H5,H8); 3.40 (m, H1,H12); 3.69 (m, H4,H9); 3.76 (m, H13,H18); 6.47 (m, H19,H20); 6.79 (s, H15,H16); 10.60 (s, H3,H10); ^{13}C NMR (DMSO) δ 35.9 (C1,C12); 37.9 (C21); 43.0 (C4,C9); 43.8 (C6,C7); 44.3 (C13,C18); 44.5 (C5,C8); 51.8 (C2,C11); 133.9 (C19,C20); 141.7 (C15,C16); 161.2 (C3,C10) 199.0 (C14,C17); HRMS requires for $C_{21}H_{18}N_2O_4$ ($M^{+\cdot}$): 362.1267, found: 362.1262.

(iii) A solution of dioxime **104** (127 mg) and dimethylacetylene dicarboxylate **40** (71 mg) in benzene (50 mL) was heated under reflux for 7 days. The reaction was monitored by ^1H NMR analysis of the crude reaction mixture. After 2 days of reflux, no product was detectable and the starting materials were present. However, ^1H NMR analysis of the reaction mixture after 7 days of reflux showed broad humps indicating that the starting materials had decomposed.

(iv) To a stirred ice-cooled solution of dioxime **104** (150 mg) in dichloromethane (30 mL) was slowly added protionwise 4-phenyl-1,2,4-triazoline-3,5-dione **41** (136 mg) until a faint red coloration persisted. The solution was stirred at 0-5°C for a further 2 hours. The solvent was removed to give a residue (295 mg); the ^1H NMR analysis of this residue indicated the presence of two adducts in a 6.5:1 ratio. The products are very polar and insoluble in most solvents except DMSO and hence was not amenable to chromatography. The major adduct, 15-phenyl-13,15,17-triazooctacyclo[10.5.2.$1^{5,8}$-.$0^{2,6}$.$0^{2,11}$.$0^{4,9}$.$0^{7,11}$.$0^{13,17}$]-eicos-18-ene-3,10,14,16-tetraone-3,10-dioxime **119** (89 mg) was recrystallised from ethanol-trifluoroacetic acid: mp >360°C; IR (KBr) 3370, 1770, 1690 cm^{-1};. ^1H NMR (DMSO) δ 1.56 (d, J = 11.2 Hz, H20b); 1.90 (d, J = 10.4 Hz, H20a); 2.56 (m, H6,H7); 2.65 (m, H5,H8); 3.76 (m, H4,H9); 5.23 (m, H1,H12); 6.85 (m, H18,H19); 7.52 (m, phenyl); 10.91 (s, H3,H10); ^{13}C NMR (DMSO) δ 37.7 (C20); 42.0 (C6,C7); 42.6 (C4,C9); 44.7 (C5,C8); 49.5 (C2,C11); 50.6 (C1,C12); 126.1, 128.3, 129.1, 129.2 (phenyl); 130.1 (C18,C19); 154.8 (C14,C16); 158.3

(C3,C10); HRMS requires for $C_{21}H_{18}N_2O_4$ ($MH^{+\cdot}$): 430.1515, found: 430.1513. Anal. calcd for $C_{21}H_{18}N_2O_4.1/2H_2O$: C, 63.00%, H, 4.59%; N, 15.97%. Found: C, 63.51%, H, 4.17%; N, 15.95%.

4.1.1 Synthesis of cage ether 121

(i) by reduction of monotosylhydrazone

(a) Synthesis of monotosylhydrazone **106**

(i) *in glacial acetic acid.* To a solution of the diketone **35** (1 g, 4.46 mmole) in acetic acid (10 mL) at room temperature was added p-toluenesulphonyl hydrazine (873 mg, 4.46 mmole) in small portions with stirring. When the addition had been completed, the reaction mixture was further stirred for 2 minutes. The product which precipitated out of the reaction mixture was filtered and washed with water (2 x 100 mL) and dried over silical gel in vacuo for a day (1.472 g, 84%); hexacyclo-[10.2.1.$0^{2,11}$.$0^{4,9}$.$0^{4,14}$.$0^{9,13}$]pentadeca-5,7-diene-3,10-dione monotosylhydrazone **106**: mp 215-216°C; IR (KBr) 3450, 1625 cm^{-1}. ^1H NMR (DMSO) δ 1.59 (d, J = 11.01 Hz, H15b); 1.89 (d, J = 11.01 Hz, H15a); 2.48 (s, CH_3); 2.70, 3.71 (m, H2,H11); 2.78, 2.91 (m, H1,H12); 3.12, 3.25 (m, H13,H14); 5.40 (m, H5,H8); 6.00 (m, H6,H7); 7.47, 7.75 (m, 4H, C_6H_4); 10.73 (s, NH); ^{13}C NMR (DMSO) δ 21.1 (CH_3); 37.3 (C15); 42.8, 46.4 (C1,C12); 45.9, 53.0 (C2,C11); 48.5, 50.4 (C4,C9); 50.0, 54.0 (C13,C14); 120.7, 122.2 (C5,C8); 122.8, 124.1 (C6,C7); 127.3, 129.5, 136.2, 143.3 (C_6H_4); 162.2 (C10); 212.1 (C3); HRMS requires for $C_{22}H_{20}N_2O_3S$ ($M^{+\cdot}$): 392.1195; found: 392.1186.

(ii) *in ethanol.* A mixture of cage diketone **35** (200 mg, 0.89 mmole) and p-toluenesulphonyl hydrazine (183 mg, 0.98 mmole) was warmed to dissolve in ethanol (8 mL) for 30 mins. A white solid which precipitated out of the solution was filtered and washed with ethanol (2 mL). The solid (50.9 mg, 14.5%) was analysed by NMR spectroscopy as the monotosylhydrazone **106**. The filtrate was reduced in volume and subsequently a second white solid precipitated and was filtered and washed with ethanol (2 mL). The solid (54 mg) was shown by NMR to be the pentacyclic pyridazine

compound **134b** (see later for physical and spectral data). The solvent from the mother liquor was removed to give a residue (338 mg), the ^{1}H NMR of which indicated the material to be largely the rearrangement product **134b**.

(b) Reduction of tosylhydrazone **106** with sodium borohydride

Sodium borohydride (2.48 g, 66.1 mmole) was added slowly to a suspension of monotosylhydrazone **106** (2.62 g, 6.68 mmole) in methanol (40 mL) and the mixture was kept at 0°C. When the addition was completed, the reaction mixture was heated under reflux for 9 days. The solvent was removed under reduced pressure to give a solid residue. Water (50 mL) was added to the residue and the product(s) extracted with ether (50 mL, 3 x 25 mL). The combined ether extracts were washed with a saturated solution of sodium bicarbonate (50 mL), water (50 mL) and dried over sodium sulphate. The solvent was removed under reduced pressure to give a solid (890 mg) which was adsorbed onto silica on a radial chromatograph. Elution with a mixture of ether and petroleum ether (1:4) gave 13-oxaheptacyclo[8.5.1.$0^{2,9}$.$0^{3,8}$.$0^{3,14}$.$0^{8,12}$.$0^{11,15}$]-hexadeca-4,6-diene **121** (381 mg) which was recrystallised from a mixture of dichloromethane and petroleum ether: mp 76-77°C; IR (KBr) 3210, 3085, 2935, 1625, 1035 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 1.36 (d, J = 10.5 Hz, H16b), 1.78 (d, J = 10.5 Hz, H16a); 2.46 (br s, H1,H10); 2.69 (m, H11,H15); 2.78 (m, H2,H9); 4.50 (m, H12,H14); 5.49 (m, H4,H7); 5.63 (m, H5,H6); ^{13}C NMR ($CDCl_3$) δ 41.9 (C16); 43.7 (C1,C10); 53.5 (C3,C8); 54.1 (C2,C9); 55.5 (C11,C15); 92.2 (C12,C14); 122.7 (C5,C6); 125.0 (C4,C7); HRMS requires for $C_{15}H_{14}O$ ($M^{+\cdot}$): 210.1045, found: 210.1048. Anal. calcd for $C_{15}H_{14}O$: C, 85.68%; H, 6.71%. Found: C, 85.49%; H, 6.83%.

Further elution with a mixture of ether and petroleum ether (1:1) gave 12-(2-tosyl)hydrazino-13-oxaheptacyclo[8.5.1.$0^{2,9}$.$0^{3,8}$.$0^{3,14}$.$0^{8,12}$.$0^{11,15}$]hexadeca-4,6-diene **130** (241 mg) which was recrystallised from ethanol: mp 180-181°C; IR (KBr) 3285, 2980, 1165 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 1.31 (d, J = 10.6 Hz, H16b); 1.69 (d, J = 10.6 Hz, H16a); 2.21, 2.49 (m, H1,H10); 2.44 (s, CH_3); 2.76 (m, H11,H15); 2.81 (m, H2,H9); 4.18, 6.32 (m, NHs); 4.36 (m, H14); 5.29 (m, H7); 5.52 (m, H4); 5.69,

5.78 (m, H5,H6); 7.32, 7.82 (4H, C_6H_4); ^{13}C NMR ($CDCl_3$) δ 21.6 (CH_3); 41.4 (C16); 42.5, 44.3 (C1,C10); 52.4, 54.3 (C3,C8); 52.7, 55.0 (C11,C15); 53.9, 54.6 (C2,C9); 88.7 (C14); 119.6 (C7); 122.3, 125.4 (C5,C6); 125.4 (C4); 128.4, 129.4, 142.7, 143.9 (C_6H_4); HRMS requires for $C_{22}H_{22}N_2O_3S$ ($M^{+\cdot}$): 394.1351, found: 394.1344. Anal. calcd for $C_{22}H_{22}N_2O_3S$: C, 66.98%; H, 5.62%; N, 7.10%. Found: C, 66.68%; H, 5.71%; N, 7.01%.

(c) Sodium borohydride reduction of bridged hydrazino **130** to cage ether **121**

A mixture of **130** (98 mg, 0.25 mmole) and sodium borohydride (96 mg, 2.59 mmole) was heated under reflux in methanol (10 mL). Monitoring the reaction by t.l.c. on silica (elutant: a 1:1 mixture of petroleum ether - ether) indicated the appearance of cage ether **121** in increasing concentration in parallel with a decrease of the bridged intermediate **130**. After 9 days reflux, ^1H NMR analysis of the reaction mixture showed a 2.3:1 ratio of cage ether **121** to the bridged hydrazino **130**. The reaction was stopped and removal of the solvent gave a residue; water (20 mL) was added to the residue. The product was extracted with ether (2 x 15 mL), washed with saturated sodium bicarbonate (10mL), water (2 x 10 mL) and dried over sodium sulphate. Removal of the solvent gave a residue (37 mg) which is shown by NMR to contain a *ca.* 2.3:1 ratio of starting material **130** and cage ether **121**.

(ii) by dehydration of the *endo-endo* diol **126**

A mixture of the *endo-endo* diol **126** (224 mg, 0.98 mmole) and p-toluenesulphonic acid (40 mg) was heated under reflux in benzene (30 mL) with slow azeotropic distillation of water/benzene using a Dean and Stark trap. The reaction progress was monitored by t.l.c. The formation of cage ether **121** steadily increased for the first 36 hours, but after 72 hours, there was an apparent decrease in the intensity of the ether with concommitant appearance of another less polar compound. The reaction was stopped, and ^1H NMR analysis of the crude reaction mixture showed that the cage ether was formed in *ca.* 20% yield together with an unidentified aromatic rearrangement product and unreacted *endo-endo* diol **126**. Attempted chromatographic separation of the

cage ether **121** from the aromatic rearrangement compound was unsucessful, since both compounds are relatively non-polar and of very similar R_f.

Attempted synthesis of a furan derivative from an acyclic tosylhydrazone 131

(i) Synthesis of the tosylhydrazone of 5-hydroxy-2-pentanone

A mixture of 5-hydroxy-2-pentanone (1.00 g, 9.79 mmole) and tosylhydrazide (2.01 g, 10.77 mmole) was dissolved by warming in ethanol (7 mL). The mixture was kept in solution for 5 mins. On cooling, a white solid (2.184 g) precipitated and was filtered and washed with ethanol (10 mL). ^{1}H NMR of the solid **131** indicated a pure sample of one of the two possible geometrical isomers of the tosylhydrazones. ^{1}H NMR (DMSO) δ 1.65 (m, 2H); 1.86 (s, 3H, CH_3); 2.35 (t, 2H); 2.48 (s, 3H, CH_3); 3.43 (t, 2H); 7.48 (d, 2H, C_6H_4), 7.72 (d, 2H, C_6H_4). Removal of the solvent from the filtrate gave a residue (0.55 g). ^{1}H NMR analysis of the residue showed the presence of a mixture of the two isomeric tosylhydrazones; the second isomer was characterised by the following ^{1}H NMR (DMSO) data: δ 1.60 (m, 2H); 1.88 (s, 3H, CH_3); 2.22 (t, 2H); 2.50 (s, 3H, CH_3); 3.42 (t, 2H); 7.48 (d, 2H, C_6H_4) 7.72 (d, 2H, C_6H_4)

(ii) Reduction of the tosylhydrazones **131**

A mixture of **131** (1.00 g 3.70 mmole) and sodium borohydride (1.39 g, 37.3 mmole) was heated under reflux in methanol (20 mL) for 1 day. Removal of the solvent gave a residue, to which water (20 mL) was added. The product extracted with dichloromethane (50 mL, 2 x 25 mL). The combined extracts were dried over sodium sulphate and removal of the solvent gave a liquid (117 mg), which was characterised from NMR to be 1-pentanol. ^{1}H NMR ($CDCl_3$) δ 0.85 (m, 3H); 1.29 (m, 5H); 1.50 (m, 2H); 3.57 (t, 2H); ^{13}C NMR ($CDCl_3$) δ 14.0 (CH_3); 22.5, 27.9, 32.5 (3 x CH_2); 63.1 (COH). The residue was similarly reduced to give a liquid product (22 mg) which was analysed by NMR as 1-pentanol. No evidence could be found for the formation of 2-methyl furan in either reaction.

Rearrangement reactions of cage monotosylhydrazone 106

(i) in ethanol

The tosylhydrazone **106** (150 mg) was heated under reflux in ethanol for 2 hours. The reaction mixture was cooled, poured into sodium carbonate solution (10% v/v, 10 mL) and extracted with dichloromethane (2 x 20 mL). The combined extracts were washed with water (2 x 10 mL) and dried over sodium sulphate. Removal of the solvent gave a residue (84 mg, 78%). The ^{1}H NMR spectrum indicated the compound to be the pentacyclic pyridazine derivative (**134a**). The residue was recrystallised from ethanol: mp 185-186°C; IR (KBr) 3190, 2890, 1620 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 1.30 (t, 3H, $OCH_2C\underline{H}_3$); 1.79, 1.87 (ABq, J = 10.3 Hz, H17a,H17b); 2.92 (br s, $W_{h/2}$ = 4 Hz, H2,H9); 3.03 , 3.21 (br s, $W_{h/2}$ = 8 Hz, H1,H10); 3.70 (m, H11,H16); 3.76 (m, $OC\underline{H}_2CH_3$) 6.71 (s, NH); 6.96 (t, H4); 7.12 (m, H5,H6,H7); ^{13}C NMR ($CDCl_3$) δ 14.3 ($OCH_2\underline{C}H_3$); 39.2, 41.3 (C2,C9); 43.8 (C1,C10); 44.3 (C17); 49.1, 49.2 (C11,C16); 61.6 ($O\underline{C}H_2CH_3$); 124.1 (C4); 126.5 (C7); 127.3, 127.4 (C5,C6); 154.9 (C15); 166.8 (C12); HRMS requires for $C_{17}H_{18}N_2O_2$ ($M^{+\cdot}$): 282.1369, found: 282.1366. Anal. calcd for $C_{17}H_{18}N_2O_2$: C,72.32%; H, 6.43%; N, 9.92%. Found: C, 72.25%; H, 6.38%; N, 10.32%.

(ii) in methanol

The tosylhydrazone **106** (150 mg) was heated under reflux in methanol for 2 hours. The reaction mixture was treated in the same manner as in the previous reaction. The rearrangement product (85 mg, 82%), the pentacyclic pyridazine derivative (**134b**) was obtained. The crude product was recrystallised from ethanol: mp 170-171°C; IR (KBr) 3180, 2930, 1630 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 1.81, 1.89 (ABq, J = 10.3 Hz, H17a, H17b); 2.93 (br s, $W_{h/2}$ = 6 Hz, H2,H6); 3.03, 3.22 (br s, $W_{h/2}$ = 8 Hz, $W_{h/2}$ = 10 Hz, H1,H8); 3.50 (s, OCH_3); 3.72 (m, H11,H16); 6.64 (s, NH); 7.01 (m, H4); 7.15 (m, H5,H6,H7); ^{13}C NMR ($CDCl_3$) δ 39.1, 41.3 (C2,C9); 43.8 (C1,C10); 44.3 (C17); 49.1, 49.2 (C11,C16); 53.2 (OCH_3); 124.2 (C4); 126.6 (C7); 127.3, 127.5 (C5,C6); 155.1 (C15); 166.8 (C12); HRMS requires for $C_{16}H_{16}N_2O_2$ ($M^{+\cdot}$): 262.1212,

found: 262.1207. Anal. calcd for $C_{16}H_{16}N_2O_2$: C, 71.89%; H, 5.66%; N, 10.48%. Found: C, 71.40%; H, 6.00%; N, 10.70%.

(iii) on storage.

On standing over a period of three months, the monotosylhydrazone **106** undergoes hydrolytic rearrangement to the corresponding hydroxy derivative **134c**: mp 313 -314°C; IR (KBr) 3507, 1631, 1443, 1367 cm^{-1}. ^1H NMR ($CDCl_3$-CF_3COOH) δ 1.93, 2.03 (ABq, J = 10.7 Hz, H17a,H17b); 3.20, 3.30 (br s, $W_{h/2}$ = 6 Hz, $W_{h/2}$ = 9 Hz, H2,H9,H1,H10); 3.82 (br s, $W_{h/2}$ = 9 Hz, H11,H16); 7.11 (m, 4H, H4,H5,H6,H7); ^{13}C NMR ($CDCl_3$-CF_3COOH) δ 41.3 (C2,C9); 44.2 (C17); 44.4 (C1,C10); 49.0 (C11,C16); 126.2, 128.3 (C4,C5,C6,C7); 146.9 (C15); 167.9 (C12). HRMS requires for $C_{15}H_{14}N_2O_2$ ($M^{+\cdot}$): 254.1055, found: 254.1052. Anal. calcd for $C_{15}H_{14}N_2O_2.1/4H_2O$: C, 69.62%; H, 5.65%; N, 10.82%. Found: C, 69.43%; H, 5.65%; N, 10.59%.

4.1.2 Reduction of diketone 35

To a stirred solution of cage diketone **35** (1g, 4.46 mmole) in dry methanol (60 mL) was added portionwise sodium borohydride (0.34 g, 9.19 mmole). The solution was stirred at room temperature for 5 hours. The solvent was removed under reduced pressure to give a residue. The product was extracted from the residue with dichloromethane (3 x 50 mL) and washed with water (20 mL). The combined extracts were dried over sodium sulphate and removal of the solvent under reduced pressure gave an oily solid; ^1H NMR of the solid indicated a 4:1 mixture of the *endo-endo* diol **126** and the *endo-exo* diol. 3-*endo*-10-*endo*-Dihydroxyhexacyclo[10.2.1.$0^{2,11}$.$0^{4,9}$.$0^{4,14}$.$0^{9,13}$]-pentadeca-5,7-diene **126**: ^1H NMR ($CDCl_3$) δ 0.92 (d, J = 10.62 Hz, H15b); 1.52 (d, J = 10.7 Hz; H15a); 2.38, 2.43, 2.77 (m, 6H, H1,H2,H11,H12,H13,H14); 3.55 (s, H3,H10), 5.21 (br s, $W_{h/2}$ = 11 Hz, OH); 5.37 (dd, J = 7.7 Hz, J = 2.7 Hz, H5,H8); 5.86 (dd, J = 7.8 Hz, J = 2.7 Hz, H6,H7); ^{13}C NMR ($CDCl_3$) δ 32.4 (C15); 42.5, 45.8, 54.1 (C1,C2,C11,C12,C13,C14); 47.4 (C4,C9); 75.9 (C3,C10); 123.9 (C5,C8); 127.9 (C6,C7). The ^1H NMR and ^{13}C NMR spectra of both diols are comparable to reported lit.[108] values.

4.1.2 Synthesis of cyclic acetal 122

A mixture of 4:1 *endo-endo* diol **126** and *endo-exo* diol from the sodium borohydride reduction of cage diketone **35** was used without purification. A solution of the diols (estimated amount of *endo-endo* diol: 0.63 g, 2.76 mmole), formalin (40% v/v, 1.0 mL, 13.36 mmole) and p-toluenesulphonic acid monohydrate (75 mg) in benzene (90 mL) was heated under reflux for 90 mins with slow azeotropic distillation of water/benzene using a Dean and Stark trap. The progress of the reaction was followed by t.l.c. analysis of the reaction mixture. The reaction was completed in 90 mins. The reaction mixture was cooled and poured into ice-cooled sodium carbonate solution (10% w/v, 50 mL) and extracted with dichloromethane (50 mL, 4 x 25 mL). The combined extracts were dried over sodium sulphate and the solvent was removed under reduced pressure to give a dark brown residue (0.83 g). The residue was adsorbed onto a silica pre-column (5 g) and eluted with dichloromethane (250 mL) to give a light brown oil (0.65 g). This oil was readsorbed onto silica on a radial chromatograph and elution with a mixture of ether-petroleum ether (1:9) gave 13,15-dioxaheptacyclo-[8.7.1.$0^{2,9}$.$0^{3,8}$.$0^{3,16}$.$0^{8,12}$.$0^{11,17}$]octadeca-4,6-diene **122** (435 mg, 66%) which was recrystallised from petroleum ether: mp 98-99°C; IR (KBr) 1574, 1491, 1256, 1179, 1138, 1073 cm^{-1}. ^1H NMR (CD_3CN) δ 1.11 (d, J = 10.7 Hz, H18b); 1.73 (d, J = 11.0 Hz, H18a); 2.52 (m, H1,H10); 2.62 (m, H11,H17); 2.83 (m, H2,H9); 3.89 (m, H12,H16); 4.86, 4.91 (ABq, J = 7.0 Hz, 2H, H14); 5.51 (m, H4,H7); 5.90 (m, H5,H6); ^{13}C NMR (CD_3CN) δ 35.0 (C18); 43.3 (C1,C10); 46.6 (C3,C8); 46.7 (C11,C17); 54.7 (C2,C9); 83.8 (C12,C16); 90.5 (C14); 124.1 (C5,C6); 129.1 (C4,C7); HRMS requires for $C_{16}H_{16}O_2$ ($M^{+\cdot}$): 240.1150, found: 240.1150. Anal. calcd for $C_{16}H_{16}O_2$: C, 79.97%; H, 6.71%. Found: C, 80.22%; H, 6.46%.

4.1.3 Synthesis of the cyclic acetonide 123

A mixture of crude *endo-endo* diol **126** (570 mg, 2.50 mmole), acetone (217 mg, 3.75 mmole) and p-toluenesulphonic acid (60 mg) was heated under reflux in benzene (50 mL) with azeotropic distillation of water/benzene for 36 hours. The reaction mixture was cooled and poured into sodium carbonate solution (10% w/v, 50 mL) and

extracted with dichloromethane (70 mL, 4 x 25 mL), washed with water (2 x 30 mL) and dried over sodium sulphate. Removal of the solvent gave a dark brown residue (671 mg) which was adsorbed onto a silica precolumn (5g) and elution with dichloromethane (250 mL) gave a light brown residue (423 mg). The residue was readsorbed onto silica on a radial chromatograph and elution with a 1:9 mixture of ether and petroleum ether gave a fraction containing largely the acetonide, 14-dimethyl-13,15-dioxaheptacyclo-[8.7.1.$0^{2,9}$.$0^{3,8}$.$0^{3,16}$.$0^{8,12}$.$0^{11,17}$]octadeca-4,6-diene **123** with a trace of the cage ether **121**. The cyclic acetonide **123** was characterised by the following NMR data: ^{1}H NMR ($CDCl_3$) δ 1.01 (d, J = 10.7 Hz, H18b); 1.30, 1.54 (s, CH_3); 1.60 (d, J = 10.8 Hz, H18a); 2.39, 2.63, 2.65 (br s, 6H, H1,H10,H11,H17,H2,H9); 3.67 (br s, $W_{h/2}$ = 5 Hz, H12,H16); 5.33 (dd, J = 7.6 Hz, 2.7 Hz, H4,H7); 5.78 (dd, J = 7.7 Hz, 2.7 Hz, H5,H6); ^{13}C NMR ($CDCl_3$) δ 26.5, 32.6 (CH_3); 34.5 (C18); 43.2 (C1,C10); 43.7 (C3,C8); 44.7 (C11,C17); 51.0 (C2,C9); 81.2 (C12,C16); 101.1 (C14); 123.5 (C5,C6); 127.5 (C4,C7). Further elution gave the cage ether **121** (14 mg) and elution with methanol gave the unreacted *endo-endo* diol **126** along with the *endo-exo* diol (243 mg).

A similar reaction was attempted but with the reaction period extended to 60 hours. Monitoring the reaction progress by ^{1}H NMR analysis showed prolonged reaction led to the formation of aromatic products along with the cage ether. ^{1}H NMR analysis after 60 hours reflux showed the product mixture to contain the acetonide **123**, diol **126**, cage ether **121** and an unidentified aromatic product in a ratio of 2:2:1:1 respectively. Chromatographic separation of the crude reaction products on silica was unsuccessful as the acetonide **123**, cage ether **121** and an unidentified aromatic rearrangement compound(s), all have very similar R_f and are quite non polar.

4.1.4 Attempted synthesis of bridged amine 124

(i) Reductive amination of cage diketone **35**

A mixture of diketone **35** (3.5 g, 15.6 mmole), ammonium bromide (15.31 g, 156.3 mmole) and sodium cyanoborohydride (0.98 g, 15.6 mmole) was stirred at room temperature in dry methanol (150 mL) at a pH of 7.5 - 8.0 under an atmosphere of dry nitrogen for 4 days. The reaction mixture was acidified with concentrated

hydrochloric acid to a pH of 2 - 3 and stirred for a further 3 days. The solvent was removed under reduced pressure to give a residue which was dissolved in water (150 mL) and extracted with dichloromethane (100 mL, 3 x 50 mL). The aqueous layer was reserved for subsequent basic extraction. The combined dichloromethane extracts were dried over sodium sulphate and the solvent was removed under reduced pressure to give a crude residue (1.83 g). The ^{1}H NMR analysis of this residue indicated a mixture of several compounds. The crude product was adsorbed onto silica on a radial chromatograph and elution with a mixture of ether-petroleum ether (1:1) gave 12-methoxy-13-oxaheptacyclo[8.5.1.$0^{2,9}$.$0^{3,8}$.$0^{3,14}$.$0^{8,12}$.$0^{11,15}$]hexadeca-4,6-diene **138** (152 mg) as an oil; IR (neat) 3013, 2954, 2860, 1572, 1443, 1067 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 1.38 (d, J = 10.6 Hz, H16b); 1.78 (d, J = 10.6 Hz, H16a); 2.52 (m, H1,H10); 2.80 (m, H2,H9,H11,H15); 3.49 (s, OCH_3); 4.35 (m, H14); 5.49 (m, H4,H7); 5.71 (m, H5,H6); ^{13}C NMR ($CDCl_3$) δ 41.6 (C16); 42.3, 44.5 (C1,C10); 50.1, 55.3 (C11,C15); 51.8 (C3,C8); 53.4 (OCH_3); 53.5, 53.8 (C2,C9); 86.7 (C14); 121.6, 124.0 (C5,C8); 122.7 (C12); 122.7, 122.9 (C6,C7); HRMS requires for $C_{16}H_{16}O_2$ ($M^{+\cdot}$): 240.1150, found: 240.1150.

Further elution with a mixture of ether and petroleum ether (4:1) gave an equilibrium mixture of the *endo*-hydroxyketone **59a** and bridged hemiacetal **59b** (670 mg). These compounds were characterised by the ^{1}H NMR spectrum which was identical to the spectrum of an authentic sample prepared by the hydrolysis of *endo*-hydroxymonoacetal **56**. Key resonance signals are: ^{1}H NMR ($CDCl_3$) δ 3.82 (d, $J_{H10,H11}$ = 3.3 Hz, C<u>H</u>OH, H10 of **59a**); 4.41 (d, $J_{H12,H11}$ = 4.9 Hz, C<u>H</u>-O-COH, H12 of **59b**).

Further elution with ether gave a fraction (156 mg) which was largely the *endo-endo* diol **126** and was characterised by the following data: ^{1}H NMR ($CDCl_3$) δ 0.92 (d, 1H); 1.55 (d, 1H); 2.38, 2.50, 2.80 (m, 6H); 3.60 (s, 2H); 5.40, 5.90 (dd, 4H).

The aqueous layer which was reserved from the previous extraction was made alkaline (pH 10 - 11) by addition of sodium hydroxide solution (10% w/v) and extracted with dichloromethane (100 mL, 3 x 50 mL). The combined extracts were dried over

sodium sulphate and the solvent removed to give a residue (1.35 g). The ^{1}H NMR analysis of this residue indicated a major product. The crude product was adsorbed onto silica on a radial chromatograph and elution with a mixture of methanol-ether (1:9) gave cage the hemiaminal, 12-hydroxy-13-azaheptacyclo[8.5.1.$0^{2,9}$.$0^{3,8}$.$0^{3,14}$.$0^{8,12}$.$0^{11,15}$]-hexadeca-4,6-diene **137b** (1.08 g) which was recrystallised from benzene: mp 173-174°C; IR (KBr) 3400, 3270, 1572, 1451 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 1.33 (d, J = 10.6 Hz, H16b); 1.73 (d, J = 10.6 Hz, H16a); 2.53 (m, H11); 2.53, 2.66 (m, H1,H10); 2.78 (m, H15); 2.90 (m, H2,H9); 3.31 (d, J = 4.5 Hz; H14); 2.4 - 3.5 (v br, NH, OH); 5.42 (m, H4); 5.57 (d, J = 8.3 Hz, H7); 5.78 (m, H5,H6); ^{13}C NMR ($CDCl_3$) δ 39.3 (C16); 42.9 (C1); 45.5 (C10); 51.6, 54.1 (C3,C8); 53.6 (C15); 54.3, 55.1 (C2,C9); 54.9 (C11); 66.5 (C14); 122.7 (C7); 123.4, 123.5 (C5,C6); 125.1 (C4); HRMS requires for $C_{15}H_{15}NO$ ($M^{+\cdot}$): 225.1154, found: 225.1155. Anal. calcd for $C_{15}H_{15}NO$: C, 79.97%; H, 6.71%; N, 6.22%. Found: C, 80.15%; H, 6.44%; N, 6.14%.

(ii) Reduction of cage hemiaminal **137b**

To a stirred solution of cage hemiaminal **137b** (138 mg, 0.61 mmole) in dry methanol (20 mL) was added portionwise sodium borohydride (115 mg, 3.11 mmole). The solution was stirred at room temperature overnight. The solvent was removed under reduced pressure to give a residue, which was dissolved in water (40 mL), extracted with dichloromethane (50 mL, 2 x 25 mL) and dried over sodium sulphate. Removal of the solvent under reduced pressure gave a solid (160 mg), the ^{1}H NMR analysis of which indicated the presence of a single product. Recrystallisation of this solid from petroleum ether-dichloromethane gave 3-*endo*-hydroxy-10-*endo*-aminohexacyclo[10.2.1.$0^{2,11}$-.$0^{4,9}$.$0^{4,14}$.$0^{9,13}$]pentadeca-5,7-diene **139**; mp 87 -88°C; IR (KBr) 3389, 3318, 3260, 3166, 1578, 1504 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 0.91 (d, J = 10.6 Hz, H15b); 1.52 (d, J = 10.62 Hz, H15a); 2.38 (m, H1,H12,H2,H11); 2.80 (m, H13,H14,H10); 3.43 (d, J = 2.5 Hz, H3); 3.2 - 4.7 (v br, NH_2, OH); 5.20 (d, J = 9.2 Hz, H8); 5.47 (d, J = 9.0 Hz; H5); 5.85 (m, H7,H6); ^{13}C NMR ($CDCl_3$) δ 32.0 (C15); 42.4 (C11); 45.0 (C2); 46.4, 46.5 (C1,C12); 48.0, 48.3 (C4,C9); 54.1, 55.4 (C13,C14); 56.3 (C10); 76.4 (C3); 122.9 (C7); 125.2 (C6); 126.5 (C8); 130.1 (C5); HRMS requires for

$C_{15}H_{17}NO$: 227.1310, found: 227.1308. $C_{15}H_{17}NO.1/3H_2O$: C, 77.22%; H, 7.63%; N, 6.00%. Found: C, 77.35%; H, 7.65%; N, 6.08%.

(iii) Acetylation of cage hemiaminal **137b**

To a stirred ice-cooled solution of hemiaminal **137b** (448 mg, 1.99 mmole) in pyridine (10 mL) was added dropwise acetic anhydride (228 mg, 2.24 mmole). When the addition was completed, the reaction mixture was allowed to warm to room temperature and stirred overnight. The reaction mixture was quenched with water (20 mL) and extracted with dichloromethane (50 mL, 25 mL). The combined extracts were washed with hydrochloric acid solution (5% v/v, 2 x 50 mL), sodium bicarbonate solution (10% w/v, 2 x 30 mL), water (50 mL) and dried over sodium sulphate. The solvent was removed under reduced pressure to give a white solid (369 mg), the ^1H NMR analysis of which showed the presence of only one product. Recrystallisation from ethyl acetate gave 10-*endo*-methylamidohexacyclo[10.2.1.$0^{2,11}$.$0^{4,9}$.$0^{4,14}$.$0^{9,13}$]-pentadeca-5,7-diene-3-one **140**; mp 156-157°C; IR (KBr) 3307, 1731, 1648, 1519 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.33 (d, J = 11.0 Hz, H15b); 1.76 (d, J = 11.0 Hz, H15a); 1.83 (s, CH_3); 2.42 (m, H2); 2.60 (m, H1); 2.72 (m, H12); 2.94 (m, H14); 3.10 (m, H13); 3.22 (m, H11); 3.62 (m, H10); 5.31 (d, J = 9.4 Hz, H8); 5.40 (m, H5, NH); 5.87 (m, H6,H7); ^{13}C NMR (CDC_3) δ 23.3 (CH_3); 36.1 (C15); 42.4 (C1); 45.6 (C12); 47.6, 51.1 (C4,C9); 50.10 (C2); 50.4 (C14); 51.5 (C1); 54.6 (C13); 56.0 (C10); 121.0 (C5); 124.3, 124.4 (C6,C7); 125.7 (C8); 171.0 ($CH_3\underline{C}O$); 218.3 (C3); HRMS requires for $C_{17}H_{17}NO_2$: C, 76.38%; H, 6.41%; N, 5.24%. Found: C, 76.41%; H, 6.25%; N, 5.16%.

(iv) Attempted dehydration of 3-*endo*-hydroxy-10-*endo*-amino cage diene **139** to the bridged amine **124**

(a) *in benzene catalysed by p-toluenesulphonic acid.* A mixture of the *endo*-aminoalcohol **139** (138 mg, 0.61 mmole) and p-toluenesulphonic acid (25 mg) was heated under reflux in benzene (20 mL) for 43 hours with azeotropic distillation of benzene/water using a Dean and Stark trap. The reaction mixture was cooled and poured

into sodium carbonate solution (10% w/v, 25 mL) and extracted with dichloromethane (50 mL, 2 x 25 mL) and dried over sodium sulphate. Removal of the solvent gave a brownish residue (117 mg). The ^{1}H NMR of the residue showed the presence of only the unreacted endo-aminoalcohol **139**.

(b) *in acidified methanol.* The *endo*-aminoalcohol **139** (18 mg) was dissolved in methanol (2 mL) and the solution was acidified to pH 2 - 3 with conc. hydrochloric acid. The reaction mixture was stirred at room temperature for 19 hours or heated under reflux for 41 hours. The reaction mixture was made alkaline (pH 10 - 11) by the addition of sodium hydroxide solution (10% w/v). The solvent was removed and the residue was dissolved in water (5 mL) and the product was extracted with dichloromethane (3 x 5 mL). The combined extracts were dried over sodium sulphate and removal of the solvent gave a residue (10 mg) which was shown by NMR analysis to be unreacted starting material **139**.

(c) *in acetonitrile with triphenylphosphine dibromide and triethylamine.* A solution of triphenylphosphine dibromide was prepared by reaction of triphenylphosphine (58 mg, 0.22 mmole) in dry acetonitrile (2 mL) with a solution of bromine (0.011 mL, 0.22 mmole) in dry acetonitrile (1 mL). The *endo*-aminoalcohol **139** (50 mg, 0.22 mmole) was added to the above solution of triphenylphosphine dibromide at 0-5°C, followed by dropwise addition of a solution of triethylamine (0.06 mL, 0.5 mmole) in dry acetonitrile (1 mL). When the additon was completed, the reaction mixture was stirred at room temperature for 15 hours. The by-product, triethylamine hydrobromide precipitated and was filtered off. Removal of the solvent from the filtrate gave a residue, the ^{1}H NMR of which indicated the formation of an unidentified unsymmetrical cage diene; the symmetrical bridged amine **124** was not observed.

(d) *in triphenylphosphine and diethylazodicarboxylate.* A mixture of triphenylphosphine (300 mg, 1.14 mmole) and diethylazodicarboxylate (200 mg, 1.14 mmole) was added to a solution of the *endo*-aminoalcohol **139** (260 mg, 1.14 mmole) in dichloromethane (10 mL). The reaction mixture was stirred at room temperature overnight. The reaction mixture was poured into water (30 mL), extracted with

dichloromethane (50 mL, 2 x 25 mL). The combined extracts were dried over sodium sulphate. Removal of the solvent gave a crude residue (573 mg); ^{1}H NMR of the residue indicated an unidentified unsymmetrical diene product, the symmetrical amine **124** was not observed.

(v) Meerwein-Ponndorf-Verley reductions

(a) *of the hemiaminal 137b*. A mixture of the hemiaminal **137b** (225 mg, 1.0 mmole) and aluminium isopropoxide (613 mg, 3.0 mmole) was heated in dry isopropanol (20 mL) for 12 hours and acetone/isopropanol was slowly distilled off at the rate of *ca.* 1 drop per minute. Dry isopropanol was added as necessary to the reaction mixture to maintain a volume of *ca.* 20 - 30 mL. The reaction mixture was cooled and removal of the solvent gave a residue, which was dissolved in hydrochloric acid solution (10% v/v, 30 mL) and extracted with dichloromethane (4 x 25 mL). The combined extracts were dried over sodium sulphate and removal of the solvent gave a residue (28 mg), the ^{1}H NMR of which indicated polymeric material. The aqueous layer from the previous extraction was made alkaline to pH 10 - 11 with sodium hydroxide solution (10% w/v) and was re-extracted with dichloromethane (4 x 25 mL). The combined extracts were dried over sodium sulphate and removal of the solvent gave a second residue (199 mg), the ^{1}H NMR of which indicated unreacted hemiaminal **137b**.

(b) *of cage diketone 35*. A mixture of cage diketone **35** (224 mg, 1.0 mmole) and aluminium isopropoxide (613 mg, 3.0 mmole) in dry isopropanol (20 mL) was reacted and the product was isolated in the same manner as in (a). Removal of the solvent gave a residue (240 mg), the ^{1}H NMR analysis of which indicated the presence of unreacted diketone **35** together with three compounds as evidenced from the three sets of AB-quartets in the region of the spectrum between 1.3 to 2.1 p.p.m. A trace of the *exo-endo* diol was also seen in this spectrum. The residue (160 mg) was adsorbed onto silica on a radial chromatograph and elution with dichloromethane gave unreacted diketone **35** (17 mg). Further elution with a 1:49 mixture of methanol and dichloromethane gave 10-*exo*-hydroxyhexacyclo[10.2.1.$0^{2,11}$.$0^{4,9}$.$0^{4,14}$.$0^{9,13}$]pentadeca-5,7-diene-3-one **143**

(51 mg) which was recrystallised from a mixture of ether and petroleum ether: mp 95-97°C; IR (KBr) 3443, 1725, 1596 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.50 (d, J = 11.0 Hz, H15b); 1.78 (d, J = 11.1 Hz, H15a); 1.68 (br s, $W_{h/2}$ = 15 Hz, OH); 2.43 (m, H2); 2.70 (m, H1,H11); 2.91 (m, H14); 3.13 (m, H12,H13); 3.92 (s, H10); 5.34 (d, J = 9.7 Hz, H5); 5.57 (d, J = 9.9 Hz, H8); 5.87 (m, H7,H6); ^{13}C NMR ($CDCl_3$) δ 35.8 (C15); 43.0 (C1); 47.2 (C12); 49.9 (C14); 51.2 (C2); 54.4 (C11); 55.5 (C13); 75.7 (C10); 120.4 (C5); 122.7 (C7); 123.5 (C8); 124.4 (C6); 216.9 (C3); HRMS requires for $C_{15}H_{14}O_2$ ($M^{+\cdot}$): 226.0994, found: 226.0997.

Further elution gave an equilibrium mixture of the *endo*-hydroxyketone **59a** and bridged hemiacetal **59b** (56 mg) as characterised by its ^1H NMR spectrum which is identical to an authentic sample. The identities of these compounds **59a** and **59b** were confirmed by conversion to their acetate derivatives.

(c) Acetylation of the crude product mixture from the Meerwein-Ponndorf-Verley reduction of cage diketone **35**.

Acetic anhydride (7 mL) was added dropwise to a solution of the crude product mixture from the Meerwein-Ponndorf-Verley reduction of diketone **35** (1.432 g) in dry pyridine (50 mL) at 0-5°C. When the addition was completed, the reaction mixture was heated at *ca.* 60°C for 3 hours. The reaction mixture was cooled and poured into water (60 mL) and the product was extracted with dichloromethane (3 x 150 mL). The combined extracts were washed with hydrochloric acid (5% v/v, 2 x 150 mL), sodium bicarbonate solution (10% w/v, 2 x 150 mL) and water (2 x 150 mL). Removal of the solvent gave a brown residue (1.40 g) which was adsorbed onto silica on a radial chromatograph. Elution with a mixture of ether and petroleum ether (1:4) gave 12-acetoxy-13-oxaheptacyclo[$8.5.1.0^{2,9}.0^{3,8}.0^{3,14}.0^{8,12}.0^{11,15}$]hexadeca-4,6-diene **145b** (41 mg) which was recrystallised from methanol: mp 80-81°C; IR (KBr) 1736, 1249 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.38 (d, J = 10.7 Hz, H16b); 1.77 (d, J = 10.8 Hz, H16a); 2.14 (s, CH_3); 2.57, 2.88, 3.04 (m, 6H, H2,H9,H1,H10,H11,H15); 4.49 (d, $J_{H14,H15}$ = 4.9 Hz, H14); 5.36 (d, J = 9.7 Hz, H4(H7)); 5.54 (d, J = 9.7 Hz, H7(H7)); 5.66 (m, H5,H6); ^{13}C NMR ($CDCl_3$) δ 21.2 (CH_3); 40.7 (C16); 44.3, 44.7, 54.1, 55.3,

56.2, 56.5 (C2,C9,C1,C10,C11,C15); 52.9, 55.0 (C3,C8); 87.1 (C14); 121.0, 122.8 (C4,C7); 122.9 (C12); 124.3, 124.5 (C5,C6); 168.4 ($CH_3\underline{C}O$); HRMS requires for $C_{17}H_{16}O_3$ ($M^{+\cdot}$): 268.1099, found: 268.1100.

Further elution gave 3-*exo*-acetoxyhexacyclo[10.2.1.$0^{2,11}$.$0^{4,9}$.$0^{4,14}$.$0^{9,13}$]-pentadeca-5,7-diene-10-one **144** (133 mg) which was recrystallised from methanol: mp 85-86°C; IR (KBr) 1736, 1372, 1231 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.48 (d, J = 11.2 Hz, H15b); 1.76 (d, J = 11.0 Hz, H15a); 2.02 (s, CH_3); 2.47 (m, H11); 2.68 (m, H12); 2.80 (m, H2); 2.89 (m, H13); 2.96 (m, H1); 3.17 (m, H14); 4.88 (s, H3); 5.36 (m, H5,H8); 5.78, 5.88 (m, H6,H7); ^{13}C NMR ($CDCl_3$) δ 20.9 (CH_3); 35.8 (C15); 42.8 (C12); 47.2 (C1); 48.4, 49.9 (C4,C9); 49.8 (C13); 51.1 (C11); 51.7 (C2); 55.8 (C14); 77.7 (C3); 120.3, 122.6 (C5,C8); 122.7, 124.2 (C6,C7); 169.9 ($CH_3\underline{C}O$); 214.7 (C10); HRMS requires for $C_{17}H_{16}O_3$ ($M^{+\cdot}$): 268.1099, found: 268.1102. Anal. calcd for $C_{17}H_{16}O_3$: C, 76.10%; H, 6.01%. Found: C, 75.96%; H, 5.86%.

Further elution gave a mixture of the *exo* and *endo* acetates **144** and **145a** (193 mg). Further elution gave 3-*endo*-acetoxyhexacyclo[10.2.1.$0^{2,11}$.$0^{4,9}$.$0^{4,14}$.$0^{9,13}$]-pentadeca-5,7-diene-10-one **145a** (510 mg) which was recrystallised from methanol: mp 83-85°C; IR (KBr) 1736, 1272, 1031 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.38 (d, J = 11.1 Hz, H15b); 1.80 (d, J = 11.1 Hz, H15a); 1.96 (s, CH_3); 2.47 (m, H11); 2.66, 2.76 (m, H12,H1); 3.02 (m, H2,H13,H14); 4.73 (d, $J_{H3,H2}$ = 3.9 Hz, H3); 5.36, 5.49 (ABq, J = 9.6 Hz, H5,H8); 5.89 (m, H6,H7); ^{13}C NMR ($CDCl_3$) δ 20.8 (CH_3); 36.5 (C15); 42.0 (C12); 44.0 (C1); 49.7 (C13); 50.0 (C11); 50.3 (C4,C9); 50.7 (C2); 53.9 (C14); 76.0 (C3); 121.0, 123.8 (C5,C8); 123.9, 125.4 (C6,C7); 170.7 ($CH_3\underline{C}O$); 214.0 (C10); HRMS requires for $C_{17}H_{16}O_3$ ($M^{+\cdot}$): 268.1099, found: 268.1100.

Further elution with a 1:1 mixture of ether and petroleum ether gave the unreacted diketone **35** (178 mg).

(vi) Reductive amination of 3-*exo*-hydroxyketone **143**

(a) *uncatalysed.* A mixture of the *exo*-hydroxyketone **143** (40 mg, 0.18 mmole), ammonium bromide (173 mg, 1.77 mmole) and sodium cyanoborohydride (11.3 mg, 0.18 mmole) was stirred in dry methanol (10 mL) (pH 7.5 - 8) at room temperature for 3

days under an atmosphere of dry nitrogen. The reaction mixture was acidified to a pH of 3 by addition of conc. hydrochloric acid and further stirred for 15 hours. Removal of the solvent gave a residue which was dissolved in water (20 mL) and extracted with dichloromethane (3 x 20 mL). The aqueous layer was reserved for a latter basic extraction. The combined extracts were dried over sodium sulphate and removal of the solvent gave a solid (43 mg), the ^{1}H NMR of which indicated a mixture of *endo-endo* diol **126** and *endo-exo* diol.

The reserved aqueous layer was made alkaline to a pH of 10 - 11 by addition of sodium hydroxide solution (10% w/v) and the product extracted with dichloromethane (3 x 20 mL). The combined extracts were dried over sodium sulphate and removal of the solvent gave a residue (3 mg), the ^{1}H NMR of which indicated polymeric materials.

(b) *with titanium isopropoxide as a catalyst.* A mixture of *exo*-hydroxyketone (200 mg, 0.29 mmole), ammonium bromide (56 mg, 0.57 mmole) and titanium isopropoxide (0.5 mL, 1.68 mmole) was stirred under an atmosphere of dry nitrogen. Monitoring the reaction mixture for the disappearance of the carbonyl peak by infrared spectroscopy indicated there was no change in the composition of the reaction mixture even after prolonged reaction overnight. A solution of sodium cyanoborohydride in dry methanol (5 mL) was added to the above mixture and was stirred at room temperature for a day. The reaction was treated in the same manner as the uncatalysed reaction. ^{1}H NMR of the crude product indicated largely unreacted *exo*-hydroxyketone **143** and a mixture of the diols.

(vii) Attempted synthesis of the Schiff base **146**

A mixture of *exo*-hydroxyketone **143** (158 mg, 0.70 mmole) and aniline (1.33 g, 14.25 mmole) was heated under reflux for 2 days in dry benzene (25 mL) with azeotropic distillation of benzene/water using a Dean and Stark trap. The reaction mixture was cooled and washed with hydrochloric acid (5% v/v, 2 x 25 mL), water (25 mL) and dried over sodium sulphate. Removal of the solvent gave a residue (124 mg), the ^{1}H NMR analysis of which indicated an intractable mixture. Furthermore, an infrared spectral

analysis of the residue did not indicate a C=N absorption which would be expected to absorb at *ca.* 1665 cm^{-1}.

(viii) Reaction of the *exo*-hydroxyketone **143** with hydroxylamine

A mixture of crude *exo*-hydroxyketone (349 mg, 1.55 mmole), hydroxylamine hydrochloride (430 mg, 6.19 mmole) and potassium carbonate (428 mg, 3.09 mmole) was heated under reflux for 5 hours in a 2:1 mixture of ethanol and water (30 mL). The reaction mixture was cooled. Removal of the solvent gave a residue which was recrystallised from ethanol to give 3-*exo*-hydroxy[10.2.1.$0^{2,11}$.$0^{4,9}$.$0^{4,14}$.$0^{9,13}$]-pentadeca-5,7-diene-10-oxime **147** as a white solid (384 mg): mp 240-242°C; IR (KBr) 3260, 1666 cm^{-1}. ^{1}H NMR ($CDCl_3$-CF_3COOH) δ 1.51 (d, J = 11.1 Hz, H15b); 1.86 (d, J = 11.7 Hz, H15a); 2.83, 3.07, 3.60 (m, 6H, H2,H11,H1,H12,H13,H14); 3.90 (s, H3); 5.36, 5.64 (ABq, J = 9.75 Hz, H5,H8); 5.89, 6.04 (m, H6,H7); ^{13}C NMR ($CDCl_3$-CF_3COOH) δ 35.1 (C15); 42.7, 46.2, 46.6, 53.1, 53.5, 54.6 (C2,C11,C1,C12,C13,C14); 46.9, 54.3 (C4,C9); 76.8 (C3); 122.7, 123.8, 126.7 (C5,C6,C7,C8); 172.7 (C10); HRMS requires for $C_{15}H_{15}NO_2$ ($M^{+\cdot}$): 241.1103, found: 241.1102.

(ix) Attempted reduction of the exo-hydroxymono-oxime **147** to the endo-amino-*exo*-hydroxy diene **142**

Lithium aluminium hydride (46 mg, 1.2 mmole) in dry tetrahydrofuran (2 mL) was added to a solution of the *exo*-hydroxymono-oxime **147** (49 mg, 0.20 mmole) in dry tetrahydrofuran (2 mL). The reaction mixture was stirred at room temperature for an hour and heated under reflux for 3.5 hours. The reaction mixture was cooled and the excess lithium aluminium hydride was destroyed with water (4 mL) and the mixture was extracted with benzene (5 x 6 mL). The combined extracts were washed with water (10 mL) and dried over potassium hydroxide. Removal of the solvent gave a residue (12 mg), the ^{1}H NMR of which indicated unreacted mono-oxime **147**.

Repeated attempts in which the reaction mixture was heated under reflux for 8 hours or 21 hours were also unsuccessful, leading to the formation of intractable mixtures.

"Michael-type" addition reaction of hemiaminal 137b with dimethylacetylene dicarboxylate 40

A mixture of the hemiaminal **137b** (250 mg, 1.11 mmole) and dimethylacetylene dicarboxylate (242 mg, 1.70 mmole) was heated under reflux in benzene (10 mL) for 13 days. ^{1}H NMR analysis of the crude reaction mixture indicated a major diene product and traces of adducts. The solvent was removed to give a residue (494 mg) which was adsorbed onto silica on a radial chromatograph. Elution with dichloromethane gave 3-N-(1,2-bismethoxycarbonyl-1-ethenylamino)hexacyclo[10.2.1.0^{2,11}.0^{4,9}.0^{4,14}.0^{9,13}]-pentadeca-5,7-diene-10-one **148** (207 mg) which was recrystallised from a mixture of petroleum ether and dichloromethane: mp 126-127°C; IR (KBr) 3448, 3248, 1731, 1601, 1490 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 1.38 (d, J = 11.1 Hz, H15b); 1.80 (d, J = 11.1 Hz, H15a); 2.49, 2.89 (H11,H2); 2.67, 2.77 (m, H12,H1); 3.01, 3.13 (m, H13,H14); 3.68, 3.81 (s, OCH_3); 3.79 (m, H3); 5.13 (s, C=C<u>H</u>-CO_2CH_3); 5.33 (m, H5); 5.58 (m, H8); 5.96 (m, H6,H7); 7.99 (br s, $W_{h/2}$ = 10 Hz, NH); ^{13}C NMR ($CDCl_3$) δ 36.1 (C15); 42.4 (C12); 45.5 (C1); 47.1, 51.7 (C4,C9); 49.4 (C11); 50.5 (C13); 51.1, 52.7 (OCH_3); 52.7 (C2); 54.6 (C14); 59.1 (C3); 89.9 (C=<u>C</u>H-CO_2CH_3); 121.5 (C8); 123.9, 124.8 (C6,C7); 125.3 (C5); 149.0 (<u>C</u>=CHCO_2CH_3); 164.5, 169.4 (<u>C</u>O_2CH_3); 214.5 (C10); HRMS requires for $C_{21}H_{21}NO_5$ ($M^{+\cdot}$): 367.1420, found: 367.1427. Anal. calcd for $C_{21}H_{21}NO_5$: C, 68.65%; H, 5.76%; N, 3.81%. Found: C, 68.36%; H, 5.93%; N, 3.79%.

Further elution with a mixture of methanol and dichloromethane (1:49) gave a fraction (28 mg), ^{1}H NMR of which indicated an adduct which was formed from a Diels-Alder reaction of **148** with dimethylacetylene dicarboxylate **40**. The adduct was characterised by the following ^{1}H NMR ($CDCl_3$) data: δ 1.53, 1.80 (d, H17a,H17b); 2.37, 2.60, 2.79 (m, 6H, H4,H5,H6,H7,H8,H9); 3.71, 3.83, 3.84, 3.85 (s, OCH_3); 4.02 (m, H1,H12); 5.05 (C=C<u>H</u>-CO_2CH_3); 6.44, 6.75 (m, H15,H16); 7.40 (br s, NH).

4.1.5 Rearrangement of endo-endo diol 126 in triphenylphosphine dibromide and acetonitrile

To a suspension of triphenylphosphine (352 mg, 1.78 mmole) in dry acetonitrile (5 mL) at 0-5°C was added dropwise a solution of bromine (210 mg in 3.8 mL of acetonitrile). The mixture was allowed to warm to room temperature. A solution of the *endo-endo* diol **126** (150 mg, 0.66 mmole) in acetonitrile (2 mL) was added to the solution of triphenylphosphine dibromide over 5 minutes. The reaction mixture was further stirred at room temperature for 10 minutes. Removal of the solvent gave a residue (671 mg); ^{1}H NMR of the residue showed a major product which is aromatic. The residue was adsorbed onto silica on a radial chromatograph and elution with a mixture of ether and petroluem ether (1:4) to give a product tentatively assigned as **150** (84 mg); ^{1}H NMR ($CDCl_3$) δ 1.32 (d, J = 11.2 Hz, 1H); 1.56 (d, J = 11.2 Hz, 1H); 1.68 (s, 1H); 2.69 (br s, $W_{h/2}$ = 7 Hz, 1H); 2.85 (br s, $W_{h/2}$ = 10 Hz, 1H); 3.03 (m, 2H); 3.42 (m, 2H); 7.03 (m, 1H); 7.11 (m, 2H); 7.20 (m, 1H); 9.35 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 37.0; 37.5; 38.5 (CH_2); 42.5; 44.8; 51.6; 53.0; 55.4; 123.7, 123.8, 126.6, 127.4, 143.8, 147.6 (C_6H_4); 203.6 (-CHO); HRMS requires for $C_{15}H_{14}O$: 210.1045, found: 210.1044.

On standing in a solution of ether and petroleum ether **150** was slowly oxidised to the carboxylic acid derivative which was characterised by the following data: ^{1}H NMR ($CDCl_3$) δ 1.62 (d, J = 11.2 Hz, 1H); 1.67 (d, J 11.0 Hz, 1H); 1.85 (s, 1H); 2.72 (br s, $W_{h/2}$ = 8 Hz, 1H); 3.00 (m, 3H), 3.44 (m, 2H); 7.07 (m, 1H); 7.16 (m, 2H); 7.28 (m, 1H); ^{13}C ($CDCl_3$); δ 37.8; 38.7; 44.9; 45.0; 47.3; 51.4; 53.0; 123.7, 123.9, 126.6, 127.3, 142.7, 147.6 (6C, C_6H_4); 180.3 (-CO_2H); HRMS requires for $C_{15}H_{14}O_2$ ($M^{+\cdot}$): 226.0994, found: 226.0993.

4.2 Diels-Alder reactions of the cage ether 121, cyclic acetal 122 and amide 140

Diels-Alder reactions of the cage ether 121

(i) A solution of **121** (53 mg) and maleic anhydride **38** (31 mg) in benzene (4 mL) was heated under reflux for 3 days. The solvent was removed under reduced

pressure to give a solid residue. Crystallisation from dichloromethane gave 7,16-dioxanonacyclo[11.5.2.1^{4,10}.0^{2,6}.0^{2,12}.0^{3,11}.0^{5,9}.0^{8,12}.0^{14,18}]heneicosa-19-ene-15,17-dione **151** (14 mg) which was recrystallised from benzene: mp 236-237°C; IR (KBr) 1810, 1730 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 1.49 (d, J = 10.6 Hz, H21b); 1.89 (d, J = 10.6 Hz, H21a); 2.14 (m, H3,H11); 2.40 (m, H4,H10); 2.76 (m, H5,H9); 3.19 (m, H14,H18); 3.26 (m, H1,H13); 4.51 (m, H6,H8); 6.42 (m, H19,H20); ^{13}C NMR ($CDCl_3$) δ 34.6 (C1,C13); 41.4 (C4,C10,C14,C18); 43.3 (C3,C11); 43.7 (C21); 54.4 (C5,C9); 56.0 (C2,C12); 85.5 (C6,C8); 133.5 (C19,C20); 173.2 (C15,C17); HRMS requires for $C_{19}H_{16}O_4$ ($M^{+\cdot}$): 308.1049, found: 308.1048. Anal. calcd for $C_{19}H_{16}O_4$: C, 74.01%; H, 5.23%. Found: C, 73.75%; H, 4.97%.

(ii) A solution of **121** (200 mg) and dimethylacetylene dicarboxylate **40** (149 mg) in benzene (10 mL) was heated under reflux for 11 days. The solvent was removed under reduced pressure to give an oil which was adsorbed onto silica on a radial chrmatograph. Elution with a mixture of ether and petroleum ether (3:2) gave 7-oxa-14,15-bis(methoxycarbonyl)octacyclo[11.2.2.1^{4,10}.0^{2,6}.0^{2,12}.0^{3,11}.0^{5,9}.0^{8,12}]octadeca-14,16-diene **157** (201 mg) which was recrystallised from ethanol: mp 98-99°C; IR (KBr) 1720, 1640, 1070, 1020 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 1.57 (d, J = 10.5 Hz, H18b); 1.88 (d, J = 10.4 Hz, H18a); 2.20 (m, H3,H11); 2.29 (m, H4,H10); 2.67 (m, H5,H9); 3.80 (s, OCH_3); 4.03 (m, H1,H13); 4.32 (m, H6,H8); 6.29 (m, H16,H17); ^{13}C NMR ($CDCl_3$) δ 39.9 (C4,C10); 41.9 (C3,C11); 42.1 (C1,C13); 44.8 (C18); 52.2 (OCH_3); 55.1 (C5,C9); 59.4 (C2,C12); 86.0 (C6,C8); 131.2 (C16,C17); 144.1 (C14,C15); 166.8 ($\underline{C}O_2CH_3$); HRMS requires for $C_{21}H_{20}O_5$ ($M^{+\cdot}$): 352.1311, found: 352.1305. Anal. calcd for $C_{21}H_{20}O_5$: C, 71.58%; H, 5.72%. Found: C, 71.68%; H, 5.51%.

Further elution with ether-petroleum ether (3:2) gave mixtures of both facial isomers **156** and **157**. Attempts at recrystallisation failed to give a pure sample of the minor isomer. NMR spectra of an enriched mixture was obtained. The minor isomer 7-oxa-14,15-bis-(methoxycarbonyl)octacyclo[11.2.2.1^{4,10}.0^{2,6}.0^{2,12}.0^{3,11}.0^{5,9}.0^{8,12}]-octadeca-14,16-diene **156** was characterised by the following NMR data: ^{1}H NMR ($CDCl_3$) δ 1.54 (d, J = 10.4 Hz, H18b); 1.87 (d, J = 10.4 Hz, H18a); 2.05

(m, H3,H11); 2.28 (br s, $W_{h/2}$ = 8 Hz, H4,H10); 2.62 (br s, $W_{h/2}$ = 10 Hz, H5,H9); 3.75 (s, OCH_3); 4.00 (m, H1,H13); 4.36 (m, H6,H8); 6.50 (m, H16,H17); ^{13}C NMR ($CDCl_3$) δ 40.1 (C4,C10); 41.9 (C3,C11); 42.1 (C1,C13); 44.9 (C18); 52.2 (OCH_3); 54.9 (C5,C9); 59.9 (C2,C12); 85.7 (C6,C8); 134.8 (C16,C17); 142.7 (C14,C16); HRMS (isomeric mixture) requires for $C_{21}H_{20}O_5$ ($M^{+\cdot}$): 352.1311, found: 352.1314.

(iii) A solution of **121** (97 mg) and methyl propiolate **73** (175 mg) in benzene (10 mL) was heated under reflux for 49 days. The solvent was removed to give a crude residue (173 mg), ^1H NMR analysis of which showed *ca.* 4% unreacted **121** and two adducts in a 12:1 ratio. The crude product (100 mg) was adsorbed onto silica on a radial chromatograph and elution with petroleum ether gave a mixture of **161** and **160** (33 mg). ^1H NMR of the mixture indicated substantial overlap of peaks for the two compounds and chemical shift values for the minor isomer were not easily distinguishable.

Further elution with petroleum ether-ether (3:1) gave 7-oxa-14-methoxy-carbonyloctacyclo[11.2.2.$1^{4,10}$.$0^{2,6}$.$0^{2,12}$.$0^{3,11}$.$0^{5,9}$.$0^{8,12}$]octadeca-14,16-diene **161** (27 mg) which was recrystallised from a mixture of petroleum ether-dichloromethane: mp 143-144°C; IR (KBr) 1707, 1623, 1584, 1243, 1082 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.52 (d, J = 10.3 Hz, H18b); 1.87 (d, J = 10.3 Hz, H18a); 1.96 (m, H3,H11); 2.26 (m, H4,H10); 2.64 (m, H5,H9); 3.48 (m, 4H, H1,OCH_3); 4.20 (m, H13); 4.30 (m, H6, H8); 6.18 (m, H16); 6.28 (m, H17); 7.45 (H15); ^{13}C NMR ($CDCl_3$) δ 39.7, 39.9 (C4,C10); 40.1 (C13); 41.0 (C1); 42.0, 42.4 (C3,C11); 44.9 (C18); 51.7 (OCH_3); 54.8, 55.2 (C5,C9); 85.9, 86.3 (C6,C8); 130.5 (C16); 132.3 (C17); 140.7 (C14); 147.2 (C15); HRMS requires for $C_{19}H_{18}O_3$: 294.1256, found: 294.1260. Anal. calcd for $C_{19}H_{18}O_3$: C, 77.53%; H, 6.16%. Found: C, 77.35%; H, 6.07%.

(iv) To a stirred ice-cooled solution of **121** (105 mg) in dichloromethane (10 mL) was slowly added portionwise 4-phenyl-1,2,4-triazoline-3,5-dione **41** until a faint red coloration persisted. The solution was stirred at 0-5°C for 19 hours. The solvent was removed under reduced pressure to give a solid residue which was adsorbed onto silica on a radial chromatograph. Elution with a mixture of ether and petroleum ether (4:1) gave 16-phenyl-14,16,18-triaza-7-oxanonacyclo[11.5.2.$1^{4,10}$.$0^{2,6}$.$0^{3,11}$.$0^{5,9}$.$0^{8,12}$.$0^{14,18}$]-

heneicosa-19-ene-15,17-dione **167** (112 mg) which was recrystallised from ethanol: mp 256- 257°C; IR (KBr) 1780, 1720 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.74 (d, J = 10.6 Hz, H21b); 2.03 (d, J = 10.6 Hz, H21a); 2.46 (br s, H4,H10); 2.81 (m, H5,H9); 2.91 (m, H3,H11); 4.45 (m, H6,H18); 5.09 (m, H1,H13); 6.39 (m, H19,H20); 7.36, 7.45 (m, phenyl); ^{13}C NMR ($CDCl_3$) δ 40.2 (C4,C10); 41.2 (C3,C11); 45.1 (C21); 53.3 (C1,C13); 53.6 (C2,C12); 55.6 (C5,C9); 84.7 (C6,C8); 125.6, 128.2, 129.1 (phenyl); 127.9 (C19,C20); 155.8 (C15,C17); HRMS requires for $C_{23}H_{19}N_3O_3$ ($M^{+\cdot}$): 385.1426, found : 385.1431. Anal. calcd for $C_{23}H_{19}N_3O_3$: C, 71.68%; H, 4.97%; N, 10.90% Found: C, 71.35%; H, 4.89%; N, 11.19%.

Further elution with a mixture of ethyl acetate and ether (2:3) gave an isomeric mixture of **167** and **166** in a ratio of 19:1. ^1H NMR of this fraction showed no enrichment was effected. Due to substantial overlap of peaks of both compounds, the δ values for the minor isomer **166** were not easily distinguishable. HRMS on the isomeric mixture requires for $C_{23}H_{19}N_3O_3$ ($M^{+\cdot}$): 385.1426, found: 385.1432.

(v) A solution of **121** (200 mg) and nitrosobenzene **74** (179 mg) in benzene (15 mL) was heated under reflux for 9 hours. The solvent was removed to give a residue (418 mg). ^1H NMR of this residue indicated *ca.* 15% unreacted **121** and two adducts in the ratio of 15.5:1 The crude product was adsorbed onto silica on a radial chromatograph and elution with ether and petroleum ether (3:7) gave 15-phenyl-15-aza-7,14-dioxaoctacyclo[$11.2.1^{4,10}.0^{2,6}.0^{2,12}.0^{3,11}.0^{5,9}.0^{8,12}$]octadeca-16-ene **173** (133 mg) which was recrystallised from ethanol: mp 100-101°C; IR (KBr) 1615, 1500, 1090 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.75 (d, J = 10.4 Hz, H18b); 2.01 (d, J = 10.5 Hz, H18a); 2.43 (m, H4,H10); 2.76 (m, H5,H9); 3.00 (m, H3); 3.12 (m, H11); 4.32 (m, H6); 4.38 (m, H8); 4.55 (d, $J_{H13,H17}$ = 6.0 Hz, H13); 4.78 (d, $J_{H1,H16}$ = 6.28 Hz; H1); 6.02 (m, H17); 6.46 (m, H16); 6.91, 6.97, 7.20 (5H, phenyl); ^{13}C NMR ($CDCl_3$) δ 39.9, 40.3 (C4,C10); 40.8 (C3,C11); 45.1 (C18); 52.3, 54.2 (C2,C12); 55.5, 55.6 (C5,C9); 60.2 (C13); 71.9 (C1); 84.0 (C6); 85.4 (C8); 117.6, 121.9, 128.3, 152.0 (phenyl); 127.8 (C17); 128.2 (C16); HRMS requires for $C_{21}H_{19}NO_2$ ($M^{+\cdot}$): 317.1416,

found: 317.1381. Anal. calcd for $C_{21}H_{19}NO_2$: C, 79.47%; H, 6.03%; N, 4.41%. Found: C, 79.49%, H, 5.84%; N, 4.70%.

Diels-Alder reactions of the cage cyclic acetal 122

(i) A solution of **122** (80 mg) and maleic anhydride **38** (33 mg) in benzene (5 mL) was heated under reflux for 2 days. The solvent was removed to give a solid residue (113 mg), the ^{1}H NMR of which indicated the formation of a single adduct. Recrystallisation of the crude residue from benzene gave 7,9,18-trioxanonacyclo-[13.5.2.1^{4,12}.0^{2,6}.0^{2,14}.0^{3,13}.0^{5,11}.0^{10,14}.0^{16,20}]tricosa-21-ene-17,19-dione **153** (88 mg): mp 279-280°C; IR (KBr) 1834, 1774, 1488, 1235, 1100 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 1.12 (d, J = 10.8 Hz, H23b); 1.66 (d, J = 10.9 Hz, H23a); 1.99 (m, H3,H13); 2.40 (m, H14,H12); 2.56 (m, H5,H11); 3.18 (m, H1,H15); 4.05 (m, H16,H20); 4.18 (s, H6,H10); 4.75, 4.79 (ABq, J = 7.1 Hz, 2H, H8); 6.44 (m, H21,H22); ^{13}C NMR ($CDCl_3$) δ 35.7 (C23); 37.6 (C1,C15); 40.8 (C16,C20); 41.0 (C4,C12); 41.5 (C3,C13); 43.3 (C5,C11); 49.7 (C2,C14); 81.5 (C6,C10); 89.1 (C8); 133.7 (C21,C22); 173.9 (C17,C19); HRMS requires for $C_{20}H_{18}O_5$ ($M^{+\cdot}$): 338.1154, found: 338.1155. Anal. calcd for $C_{20}H_{18}O_5$: C, 71.00%; H, 5.36%. Found: C, 71.40%, H, 4.99%.

(ii) A solution of **122** (240 mg) and dimethylacetylene dicarboxylate **40** (284 mg) in benzene (10 mL) was heated under reflux for 21 days. ^{1}H NMR analysis of the reaction mixture indicated *ca.* 3% unreacted **122** and two adducts in a 9:1 ratio. The solvent was removed under reduced pressure to give a residue (515 mg) which was adsorbed onto a silica pre-column (4 g) and eluted with dichloromethane (200 mL) to give a yellowish oil (449 mg). This oil was readsorbed onto silica on a radial chromatograph and elution with a mixture of ether-petroleum ether (1:9) gave a fraction of unreacted cyclic acetal **122** (17 mg). Further elution gave the major product 7,9-dioxa-16,17-bis(methoxycarbonyl)octacyclo[13.2.2.1^{4,12}.0^{2,6}.0^{2,14}.0^{3,13}.0^{5,11}.0^{10,14}]icosa-16,18-diene **159** (269 mg) which was recrystallised from benzene: mp 149-150°C; IR (KBr) 1715, 1632, 1592, 1432, 1263 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 1.17 (d, J = 10.7 Hz, H20b);

1.63 (d, J = 12.3 Hz, H20a); 2.07 (m, H3,H13); 2.41 (m, H4,H12); 2.46 (m, H5,H11); 3.77 (s, 6H, OCH_3); 3.82 (m, H1,H15); 4.08 (s, H6,H10); 4.71 (m, H8); 6.42 (m, H18,H19); ^{13}C NMR ($CDCl_3$) δ 36.5 (C20); 40.1 (C3,C13); 41.6 (C4,C12); 42.8 (C5,C11); 44.3 (C1,C15); 52.2 (OCH_3); 56.1 (C2,C14); 80.6 (C6,C10); 90.0 (C8); 132.7 (C18,C19); 144.0 (C16,C17); 166.9 (C=O); HRMS requires for $C_{22}H_{22}O_6$ ($M^{+\cdot}$): 382.1416, found: 382.1412. Anal. calcd for $C_{22}H_{22}O_6$: C, 69.10%, H, 5.80%. Found: C, 69.38%; H, 5.59%.

Further elution with methanol gave a mixture of the major and minor isomers (1:1) (21 mg) and from the ^1H NMR of this mixture the δ values of the minor isomer **158** were discerned: ^1H NMR ($CDCl_3$) δ 1.23 (d, H20b); 1.63 (d, H20a); 1.96 (m, H3,H13); 2.41 (m, H4,H12); 2.46 (m, H5,H11); 3.75 (s, 6H, OCH_3); 3.82 (m, H1,H15); 4.68 (m, H8); 6.58 (m, H18,H19).

(iii) A solution of cyclic acetal **122** (212 mg, 0.88 mmole) and methyl propiolate **73** (158 mg, 1.88 mmole) in benzene (10 mL) was heated under reflux for 173 days. Removal of the solvent gave a residue (334 mg), the ^1H NMR of which indicated *ca.* 32% unreacted acetal **122** and two adducts in a ratio of 4:1. The residue was adsorbed onto silica on a radial chromatograph and elution with a mixture of ether and petroleum ether (1:9) gave unreacted acetal **122** (77 mg). Further elution with a 15:85 mixture of ether and petroleum ether gave the major isomer, 7,9-dioxa-16-methoxycarbonyloctacyclo[13.2.2.$1^{4,12}$.$0^{2,6}$.$0^{2,14}$.$0^{3,13}$.$0^{5,11}$.$0^{10,14}$]icosa-16,18-diene **163** (164 mg) which was recrystallised from methanol: mp 142-143°C; IR (KBr) δ 1712, 1629, 1587 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.11 (d, J = 10.6 Hz, H20b); 1.62 (d, J = 10.5 Hz, H20a); 1.76 (m, H13); 1.86 (m, H3); 2.35 (br s, $W_{h/2}$ = 10 Hz, H4,H12); 2.43 (br s, $W_{h/2}$ = 5 Hz, H5,H11); 3.56 (t, J = 6.0 Hz, H1); 3.73 (s, OCH_3); 3.99 (d, J = 6.1 Hz, H15); 4.04 (s, H6); 4.08 (s, H10); 4.70, 4.73 (dd, J = 7.0 Hz, J = 6.9 Hz, H8); 6.30 (m, H18); 6.41 (m, H19); 7.45 (dd, J = 6.4 Hz, J = 2.0 Hz, H17); HRMS requires for $C_{20}H_{20}O_4$ ($M^{+\cdot}$): 324.1361, found: 324.1363. Anal. calcd for $C_{20}H_{20}O_4$: C, 74.06%; H, 6.21%. Found: C, 74.06%; H, 6.11%.

Further elution with a 1:1 mixture of ether and petroleum ether gave the minor isomer 7,9-dioxa-16-methoxycarbonyloctacyclo[13.2.2.1^{4,12}.0^{2,6}.0^{2,14}.0^{3,13}-.0^{5,11}.0^{10,14}]icosa-16,18-diene **162** (35 mg) which was recrystallised from ether and petroleum ether: mp 75-76°C; IR (KBr) 1707, 1625, 1584 cm^{-1}. ^{1}NMR ($CDCl_3$) 1.15 (d, J = 10.6 Hz, H20b); 1.63 (d, J = 10.5 Hz, H20a); 1.92 (m, H3,H13); 2.39 (m, H4,H12,H5,H11); 3.54 (m, H1); 3.71 (s, OCH_3); 4.00 (br s, $W_{h/2}$ = 5 Hz, H15,H16); 4.04 (s, H10); 4.63 (s, H8); 6.44 (m, H18); 6.55 (m, H19); 7.36 (dd, J = 6.4 Hz, J = 1.6 Hz, H17); ^{13}C NMR ($CDCl_3$) δ 36.7 (C20); 39.9, 40.0 (C13,C3); 41.6, 41.9 (C4,C12); 41.9 (C15); 42.4, 42.6 (C5,C11); 43.4 (C1); 51.3 (OCH_3); 57.1, 58.0 (C2,C4); 80.4, 80.6 (C6,C10); 89.9 (C8); 134.3 (C18); 136.0 (C19); 137.5 (C16); 145.6 (C17); 165.7 ($\underline{C}O_2CH_3$); HRMS requires for $C_{20}H_{20}O_4$ ($M^{+\cdot}$): 324.1361, found: 324.1361.

(iv) To a stirred ice-cooled solution of **122** (122 mg) in dichloromethane (10 mL) was slowly added portionwise 4-phenyl-1,2,3-triazoline-3,5-dione **41** until a faint red coloration persisted. The solution was stirred at 0-5°C for 3 days. ^{1}H NMR analysis of the crude reaction mixture indicated *ca.* 3% unreacted acetal **122** and two adducts in the ratio of 97:3. The solvent was removed under reduced pressure to give a residue which was adsorbed onto silica on a radial chromatograph. Elution with a mixture of ether-petroleum ether (3:7) gave unreacted acetal **122** (8 mg). Further elution with a mixture of ether-petroleum ether (7:3) gave 18-phenyl-16,18,20-triaza-7,9-dioxanonacyclo-[13.5.2.1^{4,12}.0^{2,6}.0^{3,13}.0^{5,11}.0^{10,14}.0^{16,18}]tricosa-21-ene-17,19-dione **169** (153 mg) which was recrystallised from acetonitrile: mp 238-239°C; IR (KBr) 1769, 1713, 1499, 1406, 1256, 1187 cm^{-1}. ^{1}H NMR (CD_3CN) δ 1.40 (d, J = 10.7 Hz, H23b); 1.84 (d, J = 10.7 Hz, H23a); 2.63 (m, H4,H12,H5,H11); 2.74 (m, H3,H13); 4.20 (br s, $W_{h/2}$ = 5 Hz, H6,H10); 4.71, 4.83 (ABq, J = 7.2 Hz, H8); 4.93 (m, H1,H15); 6.51 (m, H21,H22); 7.50 (m, phenyl); ^{13}C NMR (CD_3CN) δ 36.6 (C23); 39.9 (C3,C13); 42.1 (C4,C12); 43.4 (C5,C11); 52.7 (C2,C14); 55.7 (C1,C15); 78.8 (C6,C10); 90.1 (C8); 126.6, 128.7, 129.3, 129.4, 132.3 (phenyl); 156.3 (C=O); HRMS requires for $C_{24}H_{21}N_3O_4$ ($M^{+\cdot}$): 415.1532, found: 415.1533. Anal. calcd for

$C_{24}H_{21}N_3O_4.1/2H_2O$: C, 67.91%; H, 5.22%; N, 9.90%. Found: C, 67.51%, H, 5.19%; N, 9.68%.

(v) A solution of **122** (200 mg) and nitrosobenzene **74** (133 mg) in benzene (10 mL) was heated under reflux for 41 hours. ^{1}H NMR analysis of the crude reaction mixture indicated *ca.* 40% unreacted acetal **122** and a single adduct. The solvent was removed under reduced pressure to give a crude residue (352 mg) which was adsorbed onto a silica pre-colunm (5 g) and eluted with dichloromethane (200 mL) to give a brown solid (324 mg). This was readsorbed onto silica on a radial chromatograph and elution with a mixture of ether-petroleum ether (1:19) gave unreacted **122** (81 mg). Further elution with ether-petroleum ether (1:4) gave 17-phenyl-17-aza-7,9,16-trioxaoctacyclo-[13.2.2.1^{4,12}.0^{2,6}.0^{2,14}.0^{3,13}.0^{5,11}.0^{10,14}]eicos-18-ene **174** (129 mg) which was recrystallised from petroleum ether-dichloromethane: mp 161-162°C dec.; IR (KBr) 1593, 1486, 1181, 1136, 1039 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 1.38 (d, J = 10.7 Hz, H20b); 1.78 (d, J = 10.6 Hz, H20a); 2.54 (m, H4,H5,H11,H12); 2.85, 2.99 (m, H3,H13); 4.02 (s, H10); 4.08 (s, H6); 4.39 (d, $J_{H1,H18}$ = 6.0 Hz, H1); 4.60 (d, $J_{H15,H19}$ = 6.0 Hz, H15); 4.73, 4.79 (ABq, J = 7.0 Hz, H8); 6.15 (m, H18); 6.55 (m, H19); 6.90, 7.00, 7.20 (5H, phenyl); ^{13}C NMR ($CDCl_3$) δ 36.8 (C20); 39.0 (C3,C13); 41.5, 41.8 (C4,C12); 43.2, 43.3 (C5,C11); 51.0, 53.4 (C2,C14); 62.1 (C1); 73.7 (C15); 78.1 (C10); 79.6 (C6); 89.9 (C8); 117.4, 121.7, 128.3, 152.3 (phenyl); 129.1, 129.2 (C18,C19); HRMS requires for $C_{22}H_{21}NO_3$ ($M^{+\cdot}$): 347.1522, found 347.1523. Anal. calcd for $C_{22}H_{21}NO_3$: C, 76.06%; H, 6.09%; N, 4.03%. Found: C, 76.14%; H, 5.97%; N, 4.17%.

Diels-Alder reactions of cage amide 140

(i) A solution of amide **140** (50 mg) and maleic anhydride **38** (33 mg) in benzene (5 mL) was heated under reflux for 14 days. The solvent was removed to give a residue (172 mg). ^{1}H NMR analysis of this residue showed *ca.* 6% unreacted amide **140** and two adducts in the ratio of 6:1. The residue was recrystallised from dichloromethane to give the major product 10-*endo*-acetamido-15-oxaoctacyclo[10.5.2.1^{5,8}.0^{2,6}.0^{2,11}.-

$0^{4,9}.0^{7,11}.0^{13,17}$]eicos-18-ene-3,14,16-trione **154** (33 mg) : mp 289-290°C IR (KBr) 3377, 1772, 1725, 1654, 1531 cm^{-1}. ^1H NMR (CD_3CN) δ 1.47 (d, J = 11.0 Hz, H20b); 1.83 (d, J = 11.0 Hz, H20a); 1.89 (s, CH_3); 2.28 (m, H6); 2.51 (m, H7,H4); 2.65 (m, H5,H8); 2.83 (m, H9); 3.17 (m, H17); 3.28 (m, H13); 3.38 (m, H1); 3.48 (m, H12); 4.15 (m, H10); 6.12 (br s, $W_{h/2}$ = 17 Hz, NH); 6.45 (m, H18); 6.58 (m, H19); ^{13}C NMR (DMSO) δ 22.9 (CH_3); 32.1 (C17); 36.7 (C13); 37.5 (C20); 39.2 (C6); 40.7 (C1); 41.3 (C5); 43.0 (C8); 45.2 (C7); 49.4 (C2); 50.2 (C4); 52.5 (C10); 52.6 (C11); 52.7 (C9); 53.8 (C12); 131.6 (C18); 135.4 (C19); 171.8, 174.0, 174.3 (C14,C16,$CH_3\underline{C}$=O); 216.2 (C3); HRMS requires for $C_{21}H_{19}NO_5$ ($M^{+\cdot}$): 365.1263, found: 365.1270. Anal. calcd for $C_{21}H_{19}NO_{5.1/4}H_2O$: C, 68.19%; H, 5.31%; N, 3.79%. Found: C, 68.10%; H, 5.23%; N, 3.85%.

(ii) A solution of amide **140** (150 mg) and dimethylacetylene dicarboxylate **40** (101 mg) in benzene (10 mL) was heated under reflux for 21 days. ^1H NMR analysis of the crude reaction mixture after this period indicated the reaction was completed with the formation of two adducts in a 1:1 ratio. The solvent was removed to give a residue (264 mg) which was adsorbed onto silica on a radial chromatograph. Elution with a mixture of methanol-dichloromethane (3:97) gave 10-*endo*-acetamido-13,14-bis(methoxycarbonyl)heptacylo[$10.2.2.1^{5,8}.0^{2,6}.0^{2,11}.0^{4,9}.0^{7,11}$]heptadeca-13,15-diene-3-one **165** (88 mg) which was recrystallised from benzene: mp 167-168°C; IR (KBr) 3330, 1713, 1672, 1542, 1437, 1284 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.51 (d, J = 11.0 Hz, H17b); 1.78 (d, J = 11.0 Hz, H17a); 1.81 (s, CH_3); 2.33 (m, H6,H4); 2.60 (m, H7,H5,H8); 2.97 (m, H9); 3.78, 3.79 (s, OCH_3); 3.97 (m, H1,H12); 4.08 (dd, $J_{H10,NH}$ = 7.5 Hz, $J_{H10,H9}$ = 3.2 Hz, H10); 5.19 (d, $J_{NH,H10}$ = 7.5 Hz, NH); 6.39 (m, H16); 6.68 (m, H15); ^{13}C NMR ($CDCl_3$) δ 23.4 (CH_3); 38.4 (C6); 38.8 (C1); 39.0 (C17); 42.1 (C5); 43.7 (C7); 43.9 (C12); 44.2 (C8); 50.0 (C4); 52.5 (OCH_3); 52.6 (C9); 53.0 (C10); 56.4 (C2); 59.6 (C11); 133.6 (C16); 134.4 (C15); 143.2, 143.4 (C13,C14); 165.9 ($\underline{C}O_2CH_3$); 169.8 ($CH_3\underline{C}O$); 218.9 (C3); HRMS requires for $C_{23}H_{23}NO_6$ ($M^{+\cdot}$): 409.1525, found: 409.1531. Anal. calcd for $C_{23}H_{23}NO_6$: C, 67.47%; H, 5.66%; N, 3.42%. Found: C, 67.78%; H, 5.90%; N, 3.52%.

Further elution gave a mixture of **165** and **164** (112 mg) which was recrystallised from methanol to give 10-*endo*-acetamido-13,14-bis(methoxycarbonyl)heptacylo-[10.2.2.1^{5,8}.0^{2,6}.0^{2,11}.0^{4,9}.0^{7,11}]heptadeca-13,15-diene-3-one **164**; mp 205-205°C; IR (KBr) 3424, 1725, 1690, 1631, 1596, 1509, 1281 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 1.50 (d, J = 11.01 Hz; H17b); 1.77 (s, CH_3); 1.81 (d, J = 11.01 Hz, H17a); 2.21 (m, H6); 2.33 (m, H4); 2.41 (m, H7); 2.57 (m, H5); 2.64 (m, H8); 3.05 (m, H9); 3.70, 3.84 (s, OCH_3); 3.97 (m, H1); 4.03 (m, H12); 4.12 (dd, $J_{H10,NH}$ = 7.1 Hz, $J_{H10,H9}$ = 3.4 Hz, H10); 5.26 (d, $J_{NH,H10}$ = 7.1 Hz, NH); 6.61 (m, H15,H16); ^{13}C NMR ($CDCl_3$) δ 23.1 (CH_3); 38.6 (C6); 39.2 (C1); 39.3 (C17); 41.8 (C5); 43.4 (C7); 43.7 (C8); 44.2 (C12); 49.7 (C4); 52.3, 52.5 (OCH_3); 52.9 (C10); 53.1 (C9); 56.9, 59.6 (C2,C11); 134.4, 134.7 (C15,C16); 142.5, 144.7 (C13,C14); 164.9, 166.1 ($\underline{C}O_2CH_3$); 170.2 ($CH_3\underline{C}O$); 218.5 (C10); HRMS requires for $C_{23}H_{23}NO_6$ ($M^{+\cdot}$): 409.1525, found: 409.1527. Anal. calcd for $C_{23}H_{23}NO_6$: C, 67.47%; H, 5.66%; N, 3.42%. Found: C, 67.77%; H, 5.89%; 3.39%.

(iii) To a stirred ice-cooled solution of the amide **140** (100 mg) in dichloromethane (7 mL) was slowly added portionwise 4-phenyl-1,2,4-triazoline-3,5-dione **41** (235 mg) until a faint red coloration persisted. The reaction mixture was stirred at 0-5°C for a further 9 days. ^{1}H NMR analysis of the reaction mixture indicated the reaction was almost completed and the presence of a single adduct. The solvent was removed to give a residue (402 mg) which was adsorbed onto silica on a radial chromatograph and elution with a mixture of methanol-dichloromethane (2:98) gave 10-*endo*-acetamido-13,15,17-triazaoctacyclo[10.5.2.1^{5,8}.0^{2,6}.0^{2,11}.0^{4,9}.0^{7,11}.0^{13,17}]eicos-18-ene-3,14,16-trione **170** (146 mg) which was recrystallised from benzene-dichloromethane: mp 271-272°C; IR (KBr) 3442. 1771, 1718, 1498, 1397 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 1.52 (d, J = 11.2 Hz, H20b); 1.91 (d, J = 11.1 Hz, H20a); 1.90 (s, CH_3); 2.36 (m, H6); 2.55 (m, H4,H7); 2.63 (m, H5); 2.74 (m, H8); 3.58 (m, H9); 4.05 (m, H10); 5.07 (m, H12); 5.16 (m, H1); 5.95 (d, J = 3.5 Hz, NH); 6.68 (m, H19,H18); 7.41 (m, phenyl); ^{13}C NMR ($CDCl_3$) δ 23.6 (CH_3); 38.1 (C20); 38.4 (C6); 41.5 (C5); 42.9 (C7); 43.8 (C8); 47.2 (C2); 49.9 (C11); 50.1 (C4); 50.5 (C1);

52.9 (C9); 54.1 (C10); 55.4 (C12); 125.3, 128.5, 129.1, 131.0 (phenyl); 129.6 (C19); 130.2 (C18); 156.8 (C14,C16); 171.1 (C=O); 212.7 (C3); HRMS requires for $C_{25}H_{22}N_4O_4$ ($M^{+\cdot}$): 442.1641, found: 442.1640. Anal. calcd for $C_{25}H_{22}N_4O_4$: C, 67.86%; H, 5.01%; N, 12.66%. Found: C, 67.68%; H, 4.96%; N, 12.47%.

5.1 Diels-Alder addition reactions to the *exo*-hydroxyketone 143

(i) A solution of **143** (37 mg) and maleic anhydride **38** (17 mg) in benzene (5 mL) was heated under reflux for 16 hours. The solvent was removed under reduced pressure to give a residue (37 mg), the ^{1}H NMR of which indicated a single adduct. The residue was recrystallised from methanol to give 10-*exo*-hydroxy-15-oxaoctacyclo-[10.5.2.1^{5,8}.0^{2,6}.0^{2,11}.0^{4,9}.0^{7,11}.0^{13,17}]eicos-18-ene-3,14,16-trione **175**: mp 284-285°C; IR (KBr) 3495, 1836, 1760, 1719 cm^{-1}. ^{1}H NMR (DMSO) δ 1.56 (d, J = 10.9 Hz, H20b); 1.78 (d, J = 10.8 Hz, H20a); 2.23 (m, H6); 2.38 (m, H4,H7); 2.67 (m, H5,H9); 2.96 (m, H8); 3.08 (m, H1); 3.23 (H12); 3.32 (dd, J = 8.8 Hz, J = 3.2 Hz, H13); 3.53 (d, J = 3.6 Hz, H10); 3.67 (dd, J = 8.8 Hz, J = 3.1 Hz, H17); 5.37 (d, J = 4.0 Hz, OH); 6.52 (m, H18,H19); ^{13}C NMR (DMSO) δ 31.8 (C1); 33.8 (C12); 37.7 (C20); 39.1 (C6); 40.4 (C17); 41.2 (C13); 41.9 (C5); 44.2 (C7); 46.1 (C8); 49.3, 55.9 (C2,C11); 51.6 (C4); 54.4 (C9); 72.2 (C10); 132.6 (C18); 133.5 (C19); 173.7, 173.8 (C14,C16); 217.1 (C3); HRMS requires for $C_{19}H_{16}O_5$ ($M^{+\cdot}$): 324.0998, found: 324.0996. Anal. calcd for $C_{19}H_{16}O_{5.1/4}H_2O$: C, 69.40%; H, 5.06%. Found: C, 69.82%; H, 5.18%.

(ii) A solution of **143** (105 mg) and dimethylacetylene dicarboxylate **40** (77 mg) in benzene (5 mL) was heated under reflux for 14 hours. ^{1}H NMR of the crude reaction mixture showed the presence of a single adduct. The solvent was removed under reduced pressure to give a crude residue (150 mg) which was recrystallised twice from methanol to give platelet, colourless crystals, 10-*exo*-hydroxy-13,14-bis(methoxycarbonyl)hepta-cyclo[10.2.2.1^{5,8}.0^{2,6}.0^{2,11}.0^{4,9}.0^{7,11}]heptadeca-13,15-diene-3-one **177** (57 mg): mp 168-169°C; IR (KBr) 3448, 1719, 1625, 1595 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 1.66 (d, J = 9.8 Hz, H17b); 1.81 (d, J = 11.0 Hz, H17a); 2.15 (m, H6); 2.28 (m, H4); 2.39

(m, H7); 2.61 (m, H5,H9); 3.05 (m, H8); 3.20 (d, J = 3.6 Hz, OH); 3.40 (d, J = 3.6 Hz, H10); 3.76, 3.80 (s, OCH_3); 3.97 (dd, J = 6.1 Hz, J = 1.6 Hz, H12); 4.02 (dd, J = 5.9 Hz, J = 1.7 Hz, H1); 6.53 (m, H16,H15); ^{13}C NMR ($CDCl_3$) δ 37.3 (C6); 38.7 (C1); 39.6 (C17); 42.4 (C5); 42.8 (C12); 42.9 (C7); 46.8 (C8); 51.1 (C4); 52.2, 52.6 (OCH_3); 53.0 (C9); 57.3, 62.0 (C2,C11); 75.5 (C10); 132.9 (C16); 134.0 (C15); 140.7, 142.4 (C13,C14); 164.5, 169.4 ($\underline{C}O_2CH_3$); 216.4 (C3); HRMS requires for $C_{21}H_{20}O_6$ ($M^{+\cdot}$): 368.1260, found: 368.1256. Anal. calcd for $C_{21}H_{20}O_6$: C, 68.47%; H, 5.47%. Found: C, 68.36%; H, 5.48%.

(iii) To a stirred ice-cooled solution of the *exo*-hydroxyketone **143** (62 mg) in dichloromethane (7 mL) was slowly added portionwise 4-phenyl-1,2,4-triazoline-3,5-dione **41** (159 mg) until a faint red coloration persisted. The reaction mixture was stirred at 0-5°C for a further 6 days. ^1H NMR analysis of the reaction mixture indicated the reaction was almost completed and the presence of a single adduct. The solvent was removed to give a residue (254 mg) which was adsorbed onto silica on a radial chromatograph and elution with a mixture of methanol-dichloromethane (1:99) gave unreacted **143** (7 mg). Further elution with a 1:49 mixture of methanol and dichloromethane gave 10-*exo*-hydroxy-15-phenyl-13,15,17-triazaoctacyclo[10.5.2.$1^{5,8}$-.$0^{2,6}$.$0^{2,11}$.$0^{4,9}$.$0^{7,11}$.$0^{13,17}$]eicos-18-ene-3,14,16-trione **179** (41 mg) which was recrystallised from acetonitrile: mp 285-286°C dec.; IR (KBr) 3413, 1760, 1701 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.64 (d, J = 11.2 Hz, H20b); 1.88 (d, J = 11.2 Hz, H20a); 2.36 (m, H6); 2.55 (m, H4,H7); 2.59 (m, H5); 2.80 (m, H9); 3.15 (m, H8); 4.10 (s, H10); 5.08 (m, H1); 5.13 (m, H12); 6.67 (m, H18,H19); 7.39 (m, phenyl); ^{13}C NMR (DMSO) δ 37.4 (C20); 37.5 (C6); 41.8 (C5); 42.4 (C7); 46.2 (C8); 47.1, 53.3 (C2,C11); 49.8, 51.7 (C1,C12); 51.3 (C4); 54.4 (C9); 72.0 (C10); 126.2, 128.5, 129.2, 131.2 (phenyl); 129.7, 130.1 (C18,C19); 155.8 (C14,C16); 213.0 (C3); HRMS requires for $C_{23}H_{19}N_3O_4$ ($M^{+\cdot}$): 401.1376, found: 401.1384. Anal. calcd for $C_{23}H_{19}N_3O_4$: C, 68.82%; H, 4.77%; N, 10.47%. Found: C, 68.64%; H, 4.87%; N, 10.15%.

Diels-Alder addition reactions to the *exo*-acetoxyketone 144

(i) A solution of **144** (50 mg) and maleic anhydride **38** (20 mg) in benzene (5 mL) was heated under reflux for 1 day. The solvent was removed under reduced pressure to give a residue (65 mg), the ^{1}H NMR of which indicated a single adduct. The residue was recrystallised from a mixture of petroleum ether and dichloromethane to give 10-*exo*-acetoxy-15-oxaoctacyclo[10.5.2.1^{5,8}.0^{2,6}.0^{2,11}.0^{4,9}.0^{7,11}.0^{13,17}]eicos-18-ene-3,14,16-trione **176**: mp 178-180°C; IR (KBr) 1787, 1737, 1712 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 1.63 (d, J = 12.4 Hz, H20b); 1.84 (d, J = 11.2 Hz, H20a); 2.13 (s, CH_3); 2.28 (m, H6); 2.47 (m, H4); 2.55 (m, H7); 2.68 (m, H5); 2.80 (m, H9); 2.98 (m, H8); 3.15 (m, H12); 3.27 (m, H1); 3.33 (dd, J = 9.0 Hz, J = 3.2 Hz, H13); 3.81 (dd, J 9.0 Hz, J = 3.2 Hz, H17); 4.81 (s, H10); 6.46 (m, H18,H19); ^{13}C NMR ($CDCl_3$) δ 21.1 (CH_3) 32.0 (C1); 34.1 (C12); 38.2 (C20); 39.6 (C6); 39.9 (C17); 40.9 (C13); 42.1 (C5); 45.0 (C7); 46.7 (C8); 40.2, 55.2 (C2,C11); 51.9 (C4); 52.1 (C9); 75.5 (C10); 132.8, 133.1(C18,C19); 170.3, 172.2, 172.3 (C14,C16, $CH_3\underline{C}O$); 215.0 (C3); HRMS requires for $C_{21}H_{18}O_6$ ($M^{+\cdot}$): 366.1103, found: 366.1110.

(ii) A solution of **144** (120 mg) and dimethylacetylene dicarboxylate **40** (77 mg) in benzene (7 mL) was heated under reflux for 1 day. ^{1}H NMR of crude reaction mixture showed the presence of a single adduct. The solvent was removed under reduced pressure to give a crude residue (211 mg) which was recrystallised from methanol to give colourless crystals, 10-*exo*-acetoxy-13,14-bis(methoxycarbonyl)heptacyclo-[10.2.2.1^{5,8}.0^{2,6}.0^{2,11}.0^{4,9}.0^{7,11}]heptadeca-13,15-diene-3-one **178** (97 mg): mp 181-182°C; IR (KBr) 1731, 1637, 1595 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 1.64 (d, J = 11.0 Hz, H17b); 1.79 (d, J = 11.1 Hz, H17a); 2.07 (s, CH_3); 2.17 (m, H6); 2.34 (m, H4); 2.48 (m, H7); 2.61 (m, H5); 2.77 (m, H9); 2.85 (m, H8); 3,67, 3.77 (s, OCH_3); 3.98 (dd, J = 5.9 Hz, J = 1.8 Hz, H12); 4.03 (dd, J = 5.9 Hz, J = 1.8 Hz, H1); 4.38 (s, H10); 6.56 (m, H16,H15); ^{13}C NMR ($CDCl_3$) δ 21.0 (CH_3); 37.6 (C6); 38.2 (C1); 39.3 (C17); 41.9 (C12); 42.2 (C5); 43.8 (C7); 46.4 (C8); 50.8 (C4); 51.6 (C9); 52.1, 52.2 (OCH_3); 57.2, 59.8 (C2,C11); 78.0 (C10); 133.4 (C16); 134.5 (C15); 140.1,

143.7 (C13,C14); 169.8 (C=O); 214.3 (C3); HRMS requires for $C_{23}H_{22}O_7$ ($M^{+\cdot}$): 410.1365, found: 410.1361. Anal. calcd for $C_{23}H_{22}O_7$: C, 67.31%; H, 5.40%. Found: C, 67.31%; H, 5.42%.

(iii) To a stirred ice-cooled solution of the *exo*-acetoxyketone **144** (107 mg) in dichloromethane (7 mL) was slowly added portionwise 4-phenyl-1,2,4-triazoline-3,5-dione **41** (468 mg) until a faint red coloration persisted. The reaction mixture was stirred at 0-5°C for a further 5 hours. ^{1}H NMR analysis of the reaction mixture indicated the presence of a single adduct. The solvent was removed to give a residue (550 mg) which was adsorbed onto silica on a radial chromatograph and elution with a mixture of methanol-ether (1:99) gave a sample (140 mg), the ^{1}H NMR (NOED) of whic indicated a mixture of the "bottom face" adduct **180** and PTAD. Attempted recrystallisations of this sample failed to give a pure sample of 10-*exo*-acetoxy-15-phenyl-13,15,17-triazaocta-cyclo[10.5.2.$1^{5,8}$.$0^{2,6}$.$0^{2,11}$.$0^{4,9}$.$0^{7,11}$.$0^{13,17}$]eicos-18-ene-3,14,16-trione **180**, which is characterised by the following NMR data: ^{1}H NMR ($CDCl_3$) δ 1.63 (d, J = 11.5 Hz, H20b); 1.86 (d, J = 11.1 Hz, H20a); 2.11 (s, CH_3); 2.36 (m, H6); 2.60 (m, H7,H4); 2.68 (m, H5); 2.99 (m, H8,H9); 4.99 (s, H10); 5.04 (t, H1(H12)); 5.09 (t, H12(H1)); 6.65 (m, H18,H19); 7.40 (m, phenyl); ^{13}C NMR ($CDCl_3$) δ 21.0 (CH_3); 37.9 (C20); 38.0, 42.0, 43.1, 46.5, 48.3, 49.4, 51.1, 51.6 (C1,C12,C6,C7,C5,C8,C4,C9); 76.1 (C10); 119.8, 125.3, 128.2, 129.7, 130.0 (phenyl); 153.8 (C14,C16); 169.9 ($CH_3\underline{C}O$); 210.8 (C10).

Crystallography

Table 7.1 lists the crystal data and X-ray experimental details for the structure determinations. Intensity data were collected with a Nicolet R3m four-circle diffractometer by using monochromatized Mo Kα radiation (λ =0.71069 Å). Cell parameters were determined by least squares refinement, the setting angles of at least 20 accurately centred reflections (2θ > 17°) being used. Throughout data collections (ω scans) the intensities of three standard reflections were monitored at regular intervals and in all cases this indicated no significant crystal decomposition. The intensities were corrected for Lorentz and polarization effects but no corrections for absorption were deemed necessary. The space groups followed from systematic absences.

The structures were solved by conventional direct methods, and refined on |F| by blocked cascade or full-matrix least-squares procedures. All non-hydrogen atoms were refined with anisotopic displacement parameters. C-H hydrogen atoms were included in calculated positions with isotropic displacement parameters approximately equal to the isotropic equivalent of their carrier carbon atoms. N-H and O-H hydrogen atoms were located from difference Fourier syntheses. The functions minimized were $\Sigma w(|F_o| - |F_c|)^2$, with $w = [\sigma^2(F_o) + gF_o^2]^{-1}$. Calculations were performed with Nova 4X or IBM PC computers using SHELXTL (Version 4.1, 1983) or SHELXTL PC (Release 4.1, 1990) respectively.

The asymmetric units of **119**, **134a** and **137b** contain two molecules of DMSO (each H-bonded to an oxime OH), one molecule of ethanol (H-bonded to the amide moiety) and half a molecule of benzene (on a centre of inversion) as solvates, respectively. The asymmetric unit of **137b** contains two independent molecules.

Final atom coordinates and bonding geometries are listed in Tables 7.2 - 7.13. Perpsective views and atom labelling are shown in Figures 7.1 - 7.6.

Table 7.1. Crystal data and X-ray experimental details.

	65	**99**	**117**	**119**	**134a**	**137b**
Formula	$C_{21}H_{26}O_3$	$C_{23}H_{21}NO_4$	$C_{21}H_{22}O_4$	$C_{27}H_{31}N_5O_6S_2$	$C_{19}H_{24}N_2O_3$	$C_{15}H_{15}NO$
Formular Weight	326.5	375.4	338.4	585.7	328.4	244.8
Crystal System	triclinic	monoclinic	orthorhombic	triclinic	monoclinic	monoclinic
Space Group	P-1	$P2_1/n$	$Pna2_1$	P-1	$P2_1/n$	$P2_1/c$
a (Å)	8.726(6)	14.146(9)	20.294(6)	8.664(4)	8.366(3)	11.145(7)
b (Å)	10.013(5)	9.287(6)	7.689(2)	11.859(5)	16.209(6)	17.235(9)
c (Å)	10.322(7)	13.683(8)	10.638(3)	13.710(5)	12.828(5)	13.027(5)
α (°)	96.26(5)	90	90	87.41(3)	90	90
β (°)	109.63(5)	105.03(5)	90	84.59(3)	106.17(3)	96.26(4)
γ (°)	91.24(5)	90	90	72.44(3)	90	90
V ($Å^3$)	842.8(9)	1736(2)	1660(1)	1336.8(9)	1671(1)	2487(2)
Z	2	4	4	2	4	8
F (000)	352	792	720	616	704	1044
μ (cm^{-1})	0.8	0.9	0.9	2.4	0.8	0.8
Crystal size (mm)	.36 x .16 x .06	.48 x .24 x .11	.38 x .36 x .03	.30 x .15 x .10	.36 x .24 x .22	.28 x .16 x .13
2θ range (°)	3-50	3-60	3-52	3-48	3-52	3-52
Unique data	2968	5044	1723	4169	3284	5274
Obs. data ($I > 3\sigma(I)$)	1104	2291	1168	2256	2070	1243
Number of parameters	217	253	226	367	223	334
g	0.00051	0.0008	0.00136	0.0008	0.00075	0.0005
Residual density ($e.Å^{-3}$)	< 0.23	< 0.28	< 0.27	< 0.46	< 0.31	< 0.24
R	0.052	0.048	0.039	0.046	0.044	0.050
wR	0.053	0.055	0.047	0.054	0.055	0.050

Table 7.2. Atomic coordinates (x 10^4) and equivalent isotropic displacement coefficients ($Å^2$ x 10^3) for **65** with e.s.d.'s in parentheses.

atom	x	y	z	U_{eq}[a]
C(1)	2005(6)	5829(5)	8830(6)	27(2)
C(2)	3537(6)	6818(5)	9231(6)	26(2)
C(3)	4303(7)	6256(5)	8173(6)	23(2)
O(3)	5650(4)	5806(3)	8435(4)	31(2)
C(4)	2940(6)	6105(5)	6791(5)	17(2)
C(5)	3229(6)	5237(5)	5630(5)	23(2)
C(6)	2746(6)	5571(5)	4359(6)	24(2)
C(7)	2002(6)	6835(5)	4010(6)	26(2)
C(8)	1800(6)	7725(5)	4989(6)	26(2)
C(9)	2192(6)	7504(5)	6458(6)	24(2)
C(10)	3079(6)	8658(5)	7606(6)	21(2)
O(81)	2290(4)	9831(3)	7170(4)	22(1)
C(81)	2788(6)	11061(5)	8132(5)	21(2)
C(82)	1571(7)	11393(5)	8843(6)	37(3)
C(83)	2909(6)	12158(5)	7264(6)	33(2)
O(82)	4796(4)	8836(3)	7937(4)	22(1)
C(84)	5404(6)	9196(5)	6868(6)	25(2)
C(85)	6171(6)	8021(5)	6344(6)	34(3)
C(86)	6666(6)	10383(5)	7506(6)	32(2)
C(11)	2770(6)	8197(5)	8854(6)	24(2)
C(12)	924(6)	7831(5)	8329(5)	21(2)
C(13)	709(6)	7065(5)	6887(5)	25(2)
C(14)	1455(6)	5705(5)	7220(6)	23(2)
C(15)	736(6)	6707(5)	9166(6)	31(2)

[a] Equivalent isotropic U defined as one third of the trace of the orthogonalized U_{ij} tensor.

Table 7.3. Bond lengths (Å) and angles (°) for **65** with e.s.d.'s in parentheses.

C(1)-C(2)	1.555(7)	C(1)-C(14)	1.557(8)	C(1)-C(15)	1.534(8)
C(2)-C(3)	1.526(9)	C(2)-C(11)	1.577(7)	C(3)-O(3)	1.222(6)
C(3)-C(4)	1.509(6)	C(4)-C(5)	1.497(8)	C(4)-C(9)	1.581(7)
C(4)-C(14)	1.560(8)	C(5)-C(6)	1.319(8)	C(6)-C(7)	1.459(7)
C(7)-C(8)	1.333(8)	C(8)-C(9)	1.481(8)	C(9)-C(10)	1.545(6)
C(9)-C(13)	1.571(8)	C(10)-O(81)	1.414(6)	C(10)-O(82)	1.422(6)
C(10)-C(11)	1.518(9)	O(81)-C(81)	1.453(6)	C(81)-C(82)	1.505(9)
C(81)-C(83)	1.514(8)	O(82)-C(84)	1.450(8)	C(84)-C(85)	1.504(8)
C(84)-C(86)	1.531(7)	C(11)-C(12)	1.538(7)	C(12)-C(13)	1.548(8)
C(12)-C(15)	1.530(8)	C(13)-C(14)	1.545(7)		

C(2)-C(1)-C(14)	100.5(5)	C(2)-C(1)-C(15)	103.3(4)
C(14)-C(1)-C(15)	103.2(4)	C(1)-C(2)-C(3)	100.4(4)
C(1)-C(2)-C(11)	102.6(4)	C(3)-C(2)-C(11)	110.6(5)
C(2)-C(3)-O(3)	126.1(5)	C(2)-C(3)-C(4)	105.4(4)
O(3)-C(3)-C(4)	127.3(5)	C(3)-C(4)-C(5)	116.5(4)
C(3)-C(4)-C(9)	110.9(4)	C(5)-C(4)-C(9)	116.9(4)
C(3)-C(4)-C(14)	101.2(5)	C(5)-C(4)-C(14)	118.1(4)
C(9)-C(4)-C(14)	89.3(4)	C(4)-C(5)-C(6)	121.4(5)
C(5)-C(6)-C(7)	122.8(5)	C(6)-C(7)-C(8)	120.6(5)
C(7)-C(8)-C(9)	124.5(5)	C(4)-C(9)-C(8)	113.6(5)
C(4)-C(9)-C(10)	111.9(4)	C(8)-C(9)-C(10)	119.0(5)
C(4)-C(9)-C(13)	89.4(4)	C(8)-C(9)-C(13)	115.8(4)
C(10)-C(9)-C(13)	102.9(5)	C(9)-C(10)-O(81)	105.5(4)
C(9)-C(10)-O(82)	116.4(4)	O(81)-C(10)-O(82)	111.6(4)
C(9)-C(10)-C(11)	101.5(4)	O(81)-C(10)-C(11)	113.8(5)
O(82)-C(10)-C(11)	107.7(4)	C(10)-O(81)-C(81)	117.1(3)
O(81)-C(81)-C(82)	111.9(4)	O(81)-C(81)-C(83)	105.6(4)
C(82)-C(81)-C(83)	110.0(4)	C(10)-O(82)-C(84)	118.1(4)
O(82)-C(84)-C(85)	110.4(4)	O(82)-C(84)-C(86)	107.6(4)
C(85)-C(84)-C(86)	110.3(4)	C(2)-C(11)-C(10)	112.5(5)
C(2)-C(11)-C(12)	103.3(4)	C(10)-C(11)-C(12)	103.9(4)
C(11)-C(12)-C(13)	100.1(4)	C(11)-C(12)-C(15)	104.1(4)
C(13)-C(12)-C(15)	103.1(4)	C(9)-C(13)-C(12)	108.1(4)
C(9)-C(13)-C(14)	90.2(4)	C(12)-C(13)-C(14)	103.8(4)
C(1)-C(14)-C(4)	109.0(4)	C(1)-C(14)-C(13)	103.2(4)
C(4)-C(14)-C(13)	91.1(4)	C(1)-C(15)-C(12)	95.6(5)

Table 7.4. Atomic coordinates (x 10^4) and equivalent isotropic displacement coefficients ($Å^2$ x 10^3) for **99** with e.s.d.'s in parentheses.

atom	x	y	z	U_{eq}[a]
C(1)	2882(2)	415(3)	5399(2)	21(1)
C(2)	2854(2)	853(3)	6486(2)	20(1)
C(3)	2264(2)	2235(3)	6270(2)	19(1)
O(3)	1497(1)	2524(2)	6463(1)	25(1)
C(4)	2749(2)	3088(3)	5596(2)	17(1)
C(5)	2245(2)	4481(3)	5163(2)	17(1)
C(6)	2441(2)	5589(3)	5994(2)	19(1)
C(7)	3382(2)	5862(3)	6369(2)	20(1)
C(8)	4037(2)	4953(3)	5919(2)	18(1)
C(9)	3859(2)	3381(3)	6118(2)	16(1)
C(10)	4161(2)	2784(3)	7195(2)	18(1)
O(10A)	5168(1)	3085(2)	7624(1)	23(1)
O(10B)	3642(1)	3338(2)	7881(1)	21(1)
C(10A)	4337(2)	3908(3)	8742(2)	29(1)
C(10B)	5284(2)	3209(3)	8687(2)	30(1)
C(11)	3972(2)	1179(3)	7000(2)	19(1)
C(12)	4470(2)	851(3)	6150(2)	21(1)
C(13)	4164(2)	2188(3)	5463(2)	19(1)
C(14)	3065(2)	1887(3)	4939(2)	19(1)
C(15)	3866(2)	-356(3)	5549(2)	26(1)
O(6)	3763(1)	5124(2)	4807(1)	21(1)
N(5)	2710(1)	4972(2)	4366(2)	18(1)
C(51)	2333(2)	6277(3)	3859(2)	20(1)
C(52)	2934(2)	7188(3)	3493(2)	22(1)
C(53)	2549(2)	8387(3)	2923(2)	28(1)
C(54)	1564(2)	8707(3)	2715(2)	32(1)
C(55)	965(2)	7794(4)	3082(3)	39(1)
C(56)	1335(2)	6584(4)	3643(2)	32(1)

[a] Equivalent isotropic U defined as one third of the trace of the orthogonalized U_{ij} tensor.

Table 7.5. Bond lengths (Å) and angles (°) for **99** with e.s.d.'s in parentheses.

C(1)-C(2)	1.553(4)	C(1)-C(14)	1.554(4)	C(1)-C(15)	1.532(4)
C(2)-C(3)	1.518(4)	C(2)-C(11)	1.585(3)	C(3)-O(3)	1.211(3)
C(3)-C(4)	1.510(4)	C(4)-C(5)	1.520(3)	C(4)-C(9)	1.571(3)
C(4)-C(14)	1.568(4)	C(5)-C(6)	1.505(4)	C(5)-N(5)	1.483(4)
C(6)-C(7)	1.322(3)	C(7)-C(8)	1.497(4)	C(8)-C(9)	1.518(4)
C(8)-O(6)	1.478(3)	C(9)-C(10)	1.528(4)	C(9)-C(13)	1.554(4)
C(10)-O(10A)	1.420(3)	C(10)-O(10B)	1.429(3)	C(10)-C(11)	1.526(4)
O(10A)-C(10B)	1.426(3)	O(10B)-C(10A)	1.427(3)	C(10A)-C(10B)	1.509(4)
C(11)-C(12)	1.538(4)	C(12)-C(13)	1.549(4)	C(12)-C(15)	1.516(4)
C(13)-C(14)	1.558(3)	O(6)-N(5)	1.462(2)	N(5)-C(51)	1.429(3)
C(51)-C(52)	1.383(4)	C(51)-C(56)	1.395(4)	C(52)-C(53)	1.387(4)
C(53)-C(54)	1.380(4)	C(54)-C(55)	1.382(5)	C(55)-C(56)	1.385(4)

C(2)-C(1)-C(14)	101.9(2)	C(2)-C(1)-C(15)	104.0(2)
C(14)-C(1)-C(15)	102.9(2)	C(1)-C(2)-C(3)	100.6(2)
C(1)-C(2)-C(11)	101.8(2)	C(3)-C(2)-C(11)	111.1(2)
C(2)-C(3)-O(3)	128.6(3)	C(2)-C(3)-C(4)	104.4(2)
O(3)-C(3)-C(4)	126.3(2)	C(3)-C(4)-C(5)	116.3(2)
C(3)-C(4)-C(9)	111.9(2)	C(5)-C(4)-C(9)	110.0(2)
C(3)-C(4)-C(14)	102.7(2)	C(5)-C(4)-C(14)	123.8(2)
C(9)-C(4)-C(14)	89.0(2)	C(4)-C(5)-C(6)	108.2(2)
C(4)-C(5)-N(5)	107.2(2)	C(6)-C(5)-N(5)	108.3(2)
C(5)-C(6)-C(7)	113.2(2)	C(6)-C(7)-C(8)	113.6(2)
C(7)-C(8)-C(9)	108.7(2)	C(7)-C(8)-O(6)	109.7(2)
C(9)-C(8)-O(6)	106.0(2)	C(4)-C(9)-C(8)	106.1(2)
C(4)-C(9)-C(10)	111.8(2)	C(8)-C(9)-C(10)	120.2(2)
C(4)-C(9)-C(13)	90.5(2)	C(8)-C(9)-C(13)	120.0(2)
C(10)-C(9)-C(13)	104.3(2)	C(9)-C(10)-O(10A)	109.0(2)
C(9)-C(10)-O(10B)	116.1(2)	O(10A)-C(10)-O(10B)	106.8(2)
C(9)-C(10)-C(11)	101.1(2)	O(10A)-C(10)-C(11)	112.0(2)
O(10B)-C(10)-C(11)	111.7(2)	C(10)-O(10A)-C(10B)	106.0(2)
C(10)-O(10B)-C(10A)	108.4(2)	O(10B)-C(10A)-C(10B)	103.3(2)
O(10A)-C(10B)-C(10A)	102.5(2)	C(2)-C(11)-C(10)	111.9(2)
C(2)-C(11)-C(12)	103.1(2)	C(10)-C(11)-C(12)	103.4(2)
C(11)-C(12)-C(13)	100.9(2)	C(11)-C(12)-C(15)	104.6(2)
C(13)-C(12)-C(15)	103.5(2)	C(9)-C(13)-C(12)	107.3(2)
C(9)-C(13)-C(14)	90.0(2)	C(12)-C(13)-C(14)	102.9(2)
C(1)-C(14)-C(4)	106.9(2)	C(1)-C(14)-C(13)	102.9(2)

C(4)-C(14)-C(13)	90.4(2)	C(1)-C(15)-C(12)	95.3(2)
C(8)-O(6)-N(5)	112.4(2)	C(5)-N(5)-O(6)	108.9(2)
C(5)-N(5)-C(51)	116.0(2)	O(6)-N(5)-C(51)	109.3(2)
N(5)-C(51)-C(52)	120.6(2)	N(5)-C(51)-C(56)	120.4(3)
C(52)-C(51)-C(56)	118.8(2)	C(51)-C(52)-C(53)	120.4(2)
C(52)-C(53)-C(54)	121.2(3)	C(53)-C(54)-C(55)	118.3(3)
C(54)-C(55)-C(56)	121.3(3)	C(51)-C(56)-C(55)	120.0(3)

Table 7.6. Atomic coordinates (x 10^4) and equivalent isotropic displacement coefficients ($Å^2$ x 10^3) for **117** with e.s.d.'s in parentheses.

atom	x	y	z	U_{eq}[a]
C(1)	1522(2)	2850(4)	14710(4)	19(1)
C(2)	2205(2)	2391(5)	14129(4)	18(1)
C(3)	2570(2)	3816(4)	13403(4)	22(1)
C(4)	3239(2)	2934(5)	13186(4)	26(1)
C(5)	3423(2)	2261(5)	14521(4)	26(1)
C(6)	2753(2)	1513(4)	14963(4)	20(1)
C(7)	2683(2)	-195(5)	14177(4)	23(1)
C(8)	3330(2)	-224(5)	13377(4)	28(1)
C(9)	3169(2)	1199(5)	12394(4)	29(1)
C(10)	2447(2)	812(5)	12040(4)	24(1)
C(11)	2137(2)	655(4)	13356(4)	18(1)
C(12)	1418(2)	-9(4)	13464(4)	19(1)
C(13)	1001(2)	1468(5)	12939(4)	20(1)
C(14)	1056(2)	2965(4)	13580(4)	20(1)
C(15)	1311(2)	1287(5)	15489(4)	24(1)
C(16)	1261(2)	-176(5)	14855(4)	23(1)
C(17)	3839(2)	630(5)	14261(5)	31(1)
C(13a)	548(2)	1113(4)	11855(4)	23(1)
O(13a)	-10(1)	614(4)	11956(3)	32(1)
O(13b)	865(1)	1290(3)	10746(3)	24(1)
C(13b)	468(2)	937(5)	9641(4)	29(1)
C(14a)	725(2)	4633(5)	13266(4)	23(1)
O(14a)	771(1)	5937(4)	13884(3)	35(1)
O(14b)	382(1)	4531(3)	12186(3)	27(1)
C(14b)	34(2)	6080(4)	11789(4)	28(1)

[a] Equivalent isotropic U defined as one third of the trace of the orthogonalized U_{ij} tensor.

Table 7.7. Bond lengths (Å) and angles (°) for **117** with e.s.d.'s in parentheses.

C(1)-C(2)	1.558(5)	C(1)-C(14)	1.532(5)	C(1)-C(15)	1.522(5)
C(2)-C(3)	1.532(5)	C(2)-C(6)	1.574(5)	C(2)-C(11)	1.574(5)
C(3)-C(4)	1.535(5)	C(4)-C(5)	1.557(6)	C(4)-C(9)	1.584(5)
C(5)-C(6)	1.550(5)	C(5)-C(17)	1.536(5)	C(6)-C(7)	1.563(5)
C(7)-C(8)	1.565(5)	C(7)-C(11)	1.555(5)	C(8)-C(9)	1.548(6)
C(8)-C(17)	1.544(6)	C(9)-C(10)	1.542(5)	C(10)-C(11)	1.540(6)
C(11)-C(12)	1.550(5)	C(12)-C(13)	1.523(5)	C(12)-C(16)	1.519(6)
C(13)-C(14)	1.342(5)	C(13)-C(13a)	1.499(6)	C(14)-C(14a)	1.486(5)
C(15)-C(16)	1.315(5)	C(13a)-O(13a)	1.200(5)	C(13a)-O(13b)	1.351(5)
O(13b)-C(13b)	1.451(5)	C(14a)-O(14a)	1.202(5)	C(14a)-O(14b)	1.346(5)
O(14b)-C(14b)	1.447(4)				

C(2)-C(1)-C(14)	104.5(3)	C(2)-C(1)-C(15)	106.8(3)
C(14)-C(1)-C(15)	107.4(3)	C(1)-C(2)-C(3)	117.9(3)
C(1)-C(2)-C(6)	120.2(3)	C(3)-C(2)-C(6)	104.4(3)
C(1)-C(2)-C(11)	108.7(3)	C(3)-C(2)-C(11)	112.7(3)
C(6)-C(2)-C(11)	89.6(3)	C(2)-C(3)-C(4)	100.8(3)
C(3)-C(4)-C(5)	102.8(3)	C(3)-C(4)-C(9)	111.9(3)
C(5)-C(4)-C(9)	103.1(3)	C(4)-C(5)-C(6)	100.9(3)
C(4)-C(5)-C(17)	103.8(3)	C(6)-C(5)-C(17)	103.5(3)
C(2)-C(6)-C(5)	106.8(3)	C(2)-C(6)-C(7)	89.7(3)
C(5)-C(6)-C(7)	103.3(3)	C(6)-C(7)-C(8)	103.1(3)
C(6)-C(7)-C(11)	90.7(3)	C(8)-C(7)-C(11)	107.3(3)
C(7)-C(8)-C(9)	100.4(3)	C(7)-C(8)-C(17)	102.9(3)
C(9)-C(8)-C(17)	104.6(3)	C(4)-C(9)-C(8)	102.5(3)
C(4)-C(9)-C(10)	112.2(3)	C(8)-C(9)-C(10)	103.2(3)
C(9)-C(10)-C(11)	100.4(3)	C(2)-C(11)-C(7)	90.0(3)
C(2)-C(11)-C(10)	111.9(3)	C(7)-C(11)-C(10)	104.6(3)
C(2)-C(11)-C(12)	108.9(3)	C(7)-C(11)-C(12)	119.4(3)
C(10)-C(11)-C(12)	118.5(3)	C(11)-C(12)-C(13)	104.5(3)
C(11)-C(12)-C(16)	107.3(3)	C(13)-C(12)-C(16)	107.7(3)
C(12)-C(13)-C(14)	114.0(3)	C(12)-C(13)-C(13a)	119.1(3)
C(14)-C(13)-C(13a)	126.7(3)	C(1)-C(14)-C(13)	113.6(3)
C(1)-C(14)-C(14a)	120.3(3)	C(13)-C(14)-C(14a)	126.0(3)
C(1)-C(15)-C(16)	114.7(4)	C(12)-C(16)-C(15)	114.3(3)
C(5)-C(17)-C(8)	95.1(3)	C(13)-C(13a)-O(13a)	124.6(4)
C(13)-C(13a)-O(13b)	111.2(3)	O(13a)-C(13a)-O(13b)	124.0(4)
C(13a)-O(13b)-C(13b)	115.1(3)	C(14)-C(14a)-O(14a)	124.2(4)
C(14)-C(14a)-O(14b)	112.1(3)	O(14a)-C(14a)-O(14b)	123.7(3)
C(14a)-O(14b)-C(14b)	117.0(3)		

Table 7.8. Atomic coordinates (x 10^4) and equivalent isotropic displacement coefficients ($Å^2$ x 10^3) for **119** with e.s.d.'s in parentheses.

atom	x	y	z	U_{eq}[a]
C(1)	4291(5)	2027(4)	7346(3)	16(2)
C(2)	5548(5)	1956(4)	6463(3)	15(2)
C(3)	7342(5)	1539(4)	6575(3)	14(2)
N(3)	7962(4)	1296(3)	7402(3)	18(1)
O(3)	9690(4)	887(3)	7238(3)	23(1)
C(4)	8129(6)	1389(4)	5535(3)	18(2)
C(5)	7129(5)	703(4)	5064(3)	17(2)
C(6)	5373(5)	1336(4)	5511(3)	17(2)
C(7)	4917(5)	2544(4)	4948(3)	16(2)
C(8)	6462(5)	2464(4)	4239(3)	18(2)
C(9)	7659(5)	2635(4)	4959(3)	18(2)
C(10)	6575(5)	3585(4)	5629(3)	15(2)
N(10)	6758(4)	4533(3)	5933(3)	17(1)
O(10)	8299(4)	4652(3)	5568(2)	21(1)
C(11)	5066(5)	3206(4)	5876(3)	15(2)
C(12)	3554(5)	4041(4)	6414(3)	15(2)
N(13)	4000(4)	4127(3)	7428(3)	15(1)
C(14)	3159(5)	4999(4)	8067(3)	17(2)
O(14)	2612(4)	6056(3)	7888(2)	24(1)
N(15)	3149(4)	4431(3)	8987(3)	15(1)
C(16)	3793(5)	3197(4)	8905(3)	18(2)
O(16)	3836(4)	2445(3)	9546(2)	20(1)
N(17)	4402(4)	3011(3)	7950(3)	15(1)
C(18)	2611(5)	2393(4)	6993(3)	19(2)
C(19)	2217(5)	3437(4)	6506(3)	17(2)
C(20)	7091(6)	1144(4)	3993(3)	20(2)
C(21)	2537(5)	5028(4)	9905(3)	18(2)
C(22)	1035(6)	5911(4)	9958(4)	22(2)
C(23)	475(6)	6509(4)	10823(4)	23(2)
C(24)	1378(6)	6228(4)	11625(4)	25(2)
C(25)	2865(6)	5342(4)	11573(3)	24(2)
C(26)	3457(5)	4744(4)	10700(3)	20(2)
S(1S)[b]	12696(2)	-271(1)	9169(1)	24(1)
O(1S)[b]	11062(4)	542(3)	8914(3)	41(1)
C(1S)[b]	12867(6)	58(4)	10398(3)	25(2)
C(2S)[b]	12414(6)	-1684(4)	9413(4)	34(2)
S(2S)[b]	8527(2)	6889(1)	7375(1)	33(1)

O(2S)[b]	8597(4)	6672(3)	6312(2)	33(1)
C(3S)[b]	9386(6)	8062(4)	7460(4)	28(2)
C(4S)[b]	6467(6)	7700(5)	7732(4)	35(2)

[a] Equivalent isotropic U defined as one third of the trace of the orthogonalized U_{ij} tensor.
[b] DMSO solvate.

Table 7.9. Bond lengths (Å) and angles (°) for **119** with e.s.d.'s in parentheses.

C(1)-C(2)	1.537(6)	C(1)-N(17)	1.493(6)	C(1)-C(18)	1.509(6)
C(2)-C(3)	1.503(6)	C(2)-C(6)	1.568(7)	C(2)-C(11)	1.613(6)
C(3)-N(3)	1.285(6)	C(3)-C(4)	1.514(6)	N(3)-O(3)	1.426(5)
C(4)-C(5)	1.552(7)	C(4)-C(9)	1.602(6)	C(5)-C(6)	1.558(6)
C(5)-C(20)	1.537(6)	C(6)-C(7)	1.555(6)	C(7)-C(8)	1.559(6)
C(7)-C(11)	1.560(6)	C(8)-C(9)	1.559(7)	C(8)-C(20)	1.535(6)
C(9)-C(10)	1.512(6)	C(10)-N(10)	1.275(6)	C(10)-C(11)	1.511(7)
N(10)-O(10)	1.427(5)	C(11)-C(12)	1.530(5)	C(12)-N(13)	1.493(6)
C(12)-C(19)	1.529(7)	N(13)-C(14)	1.369(5)	N(13)-N(17)	1.438(5)
C(14)-O(14)	1.221(5)	C(14)-N(15)	1.403(6)	N(15)-C(16)	1.405(5)
N(15)-C(21)	1.447(6)	C(16)-O(16)	1.218(5)	C(16)-N(17)	1.366(5)
C(18)-C(19)	1.344(6)	C(21)-C(22)	1.401(6)	C(21)-C(26)	1.381(7)
C(22)-C(23)	1.381(7)	C(23)-C(24)	1.381(7)	C(24)-C(25)	1.393(6)
C(25)-C(26)	1.393(6)	S(1S)-O(1S)	1.515(3)	S(1S)-C(1S)	1.776(5)
S(1S)-C(2S)	1.778(5)	S(2S)-O(2S)	1.485(4)	S(2S)-C(3S)	1.776(6)
S(2S)-C(4S)	1.786(5)				

C(2)-C(1)-N(17)	105.3(4)	C(2)-C(1)-C(18)	109.2(4)
N(17)-C(1)-C(18)	107.1(3)	C(1)-C(2)-C(3)	121.6(4)
C(1)-C(2)-C(6)	119.0(4)	C(3)-C(2)-C(6)	103.8(3)
C(1)-C(2)-C(11)	108.3(3)	C(3)-C(2)-C(11)	110.4(4)
C(6)-C(2)-C(11)	88.8(3)	C(2)-C(3)-N(3)	124.1(4)
C(2)-C(3)-C(4)	104.6(4)	N(3)-C(3)-C(4)	131.0(4)
C(3)-N(3)-O(3)	109.4(3)	C(3)-C(4)-C(5)	102.0(4)
C(3)-C(4)-C(9)	109.9(3)	C(5)-C(4)-C(9)	102.8(4)
C(4)-C(5)-C(6)	101.6(3)	C(4)-C(5)-C(20)	104.2(4)
C(6)-C(5)-C(20)	102.8(3)	C(2)-C(6)-C(5)	106.8(4)
C(2)-C(6)-C(7)	90.9(3)	C(5)-C(6)-C(7)	103.3(3)

C(6)-C(7)-C(8)	103.2(3)	C(6)-C(7)-C(11)	91.2(3)
C(8)-C(7)-C(11)	107.1(4)	C(7)-C(8)-C(9)	101.3(3)
C(7)-C(8)-C(20)	102.9(4)	C(9)-C(8)-C(20)	104.5(3)
C(4)-C(9)-C(8)	102.0(4)	C(4)-C(9)-C(10)	109.8(3)
C(8)-C(9)-C(10)	102.7(3)	C(9)-C(10)-N(10)	131.6(4)
C(9)-C(10)-C(11)	104.4(4)	N(10)-C(10)-C(11)	123.9(4)
C(10)-N(10)-O(10)	110.7(3)	C(2)-C(11)-C(7)	89.1(3)
C(2)-C(11)-C(10)	109.0(3)	C(7)-C(11)-C(10)	104.4(3)
C(2)-C(11)-C(12)	108.8(3)	C(7)-C(11)-C(12)	120.5(4)
C(10)-C(11)-C(12)	120.4(4)	C(11)-C(12)-N(13)	105.7(3)
C(11)-C(12)-C(19)	108.0(4)	N(13)-C(12)-C(19)	106.7(3)
C(12)-N(13)-C(14)	124.1(3)	C(12)-N(13)-N(17)	113.1(3)
C(14)-N(13)-N(17)	108.8(3)	N(13)-C(14)-O(14)	127.5(4)
N(13)-C(14)-N(15)	105.2(3)	O(14)-C(14)-N(15)	127.2(4)
C(14)-N(15)-C(16)	111.3(3)	C(14)-N(15)-C(21)	124.7(3)
C(16)-N(15)-C(21)	123.9(3)	N(15)-C(16)-O(16)	127.9(4)
N(15)-C(16)-N(17)	105.3(4)	O(16)-C(16)-N(17)	126.8(4)
C(1)-N(17)-N(13)	112.2(3)	C(1)-N(17)-C(16)	124.7(4)
N(13)-N(17)-C(16)	108.8(3)	C(1)-C(18)-C(19)	114.4(5)
C(12)-C(19)-C(18)	114.0(4)	C(5)-C(20)-C(8)	95.3(3)
N(15)-C(21)-C(22)	118.9(4)	N(15)-C(21)-C(26)	119.7(4)
C(22)-C(21)-C(26)	121.3(4)	C(21)-C(22)-C(23)	119.0(4)
C(22)-C(23)-C(24)	120.2(4)	C(23)-C(24)-C(25)	120.6(4)
C(24)-C(25)-C(26)	119.8(4)	C(21)-C(26)-C(25)	119.0(4)
O(1S)-S(1S)-C(1S)	105.3(2)	O(1S)-S(1S)-C(2S)	105.9(2)
C(1S)-S(1S)-C(2S)	97.0(3)	O(2S)-S(2S)-C(3S)	105.6(2)
O(2S)-S(2S)-C(4S)	106.0(2)	C(3S)-S(2S)-C(4S)	97.5(2)

Table 7.10. Atomic coordinates (x 10^4) and equivalent isotropic displacement coefficients ($Å^2$ x 10^3) for **134a** with e.s.d.'s in parentheses.

atom	x	y	z	U_{eq}[a]
C(1)	5121(3)	4741(1)	3282(2)	20(1)
C(2)	6908(3)	4478(1)	3923(2)	21(1)
C(3)	8046(3)	3971(1)	3419(2)	21(1)
C(4)	8418(3)	3180(2)	3162(2)	24(1)
C(5)	9777(3)	3108(2)	2733(2)	27(1)
C(6)	10713(3)	3787(2)	2599(2)	28(1)
C(7)	10366(3)	4583(2)	2892(2)	25(1)
C(8)	8996(3)	4651(1)	3304(2)	21(1)
C(9)	7994(3)	5246(2)	3811(2)	22(1)
C(10)	6690(3)	5870(1)	3146(2)	21(1)
C(11)	5959(3)	5599(1)	1952(2)	19(1)
C(12)	7200(3)	5495(1)	1295(2)	20(1)
O(12)	8185(2)	6057(1)	1255(1)	27(1)
N(13)	7121(2)	4802(1)	719(2)	20(1)
N(14)	6224(2)	4080(1)	795(1)	19(1)
C(15)	5301(3)	4100(1)	1438(2)	19(1)
C(16)	4904(3)	4828(1)	2042(2)	19(1)
C(17)	5216(3)	5664(1)	3601(2)	23(1)
O(15)	4482(2)	3407(1)	1582(1)	23(1)
C(18)	4715(3)	2698(1)	942(2)	25(1)
C(19)	3991(3)	1959(2)	1348(2)	30(1)
O(1S)[b]	11121(2)	5953(1)	660(2)	37(1)
C(1S)[b]	11769(3)	6763(2)	870(2)	31(1)
C(2S)[b]	10558(4)	7423(2)	369(3)	46(1)

[a] Equivalent isotropic U defined as one third of the trace of the orthogonalized U_{ij} tensor.

[b] Ethanol solvate.

Table 7.11. Bond lengths (Å) and angles (°) for **134a** with e.s.d.'s in parentheses.

C(1)-C(2)	1.552(3)	C(1)-C(16)	1.557(3)	C(1)-C(17)	1.546(3)
C(2)-C(3)	1.530(4)	C(2)-C(9)	1.572(3)	C(3)-C(4)	1.380(3)
C(3)-C(8)	1.391(3)	C(4)-C(5)	1.399(4)	C(5)-C(6)	1.390(4)
C(6)-C(7)	1.396(4)	C(7)-C(8)	1.394(4)	C(8)-C(9)	1.536(4)
C(9)-C(10)	1.556(3)	C(10)-C(11)	1.547(3)	C(10)-C(17)	1.540(4)
C(11)-C(12)	1.518(4)	C(11)-C(16)	1.554(3)	C(12)-O(12)	1.239(3)
C(12)-N(13)	1.336(3)	N(13)-N(14)	1.408(3)	N(14)-C(15)	1.278(3)
C(15)-C(16)	1.498(3)	C(15)-O(15)	1.356(3)	O(15)-C(18)	1.456(3)
C(18)-C(19)	1.500(4)	O(1S)-C(1S)	1.418(3)	C(1S)-C(2S)	1.490(4)

C(2)-C(1)-C(16)	112.8(2)	C(2)-C(1)-C(17)	99.0(2)
C(16)-C(1)-C(17)	99.5(2)	C(1)-C(2)-C(3)	123.0(2)
C(1)-C(2)-C(9)	103.2(2)	C(3)-C(2)-C(9)	86.8(2)
C(2)-C(3)-C(4)	143.9(2)	C(2)-C(3)-C(8)	93.5(2)
C(4)-C(3)-C(8)	122.5(2)	C(3)-C(4)-C(5)	115.7(2)
C(4)-C(5)-C(6)	122.0(2)	C(5)-C(6)-C(7)	122.2(3)
C(6)-C(7)-C(8)	115.4(2)	C(3)-C(8)-C(7)	122.2(2)
C(3)-C(8)-C(9)	93.3(2)	C(7)-C(8)-C(9)	144.4(2)
C(2)-C(9)-C(8)	86.4(2)	C(2)-C(9)-C(10)	103.3(2)
C(8)-C(9)-C(10)	123.9(2)	C(9)-C(10)-C(11)	112.4(2)
C(9)-C(10)-C(17)	99.5(2)	C(11)-C(10)-C(17)	100.1(2)
C(10)-C(11)-C(12)	116.0(2)	C(10)-C(11)-C(16)	103.4(2)
C(12)-C(11)-C(16)	116.3(2)	C(11)-C(12)-O(12)	120.5(2)
C(11)-C(12)-N(13)	117.6(2)	O(12)-C(12)-N(13)	121.8(2)
C(12)-N(13)-N(14)	127.3(2)	N(13)-N(14)-C(15)	116.9(2)
N(14)-C(15)-C(16)	127.9(2)	N(14)-C(15)-O(15)	119.1(2)
C(16)-C(15)-O(15)	112.9(2)	C(1)-C(16)-C(11)	104.0(2)
C(1)-C(16)-C(15)	118.5(2)	C(11)-C(16)-C(15)	112.5(2)
C(1)-C(17)-C(10)	95.6(2)	C(15)-O(15)-C(18)	115.2(2)
O(15)-C(18)-C(19)	107.7(2)	O(1S)-C(1S)-C(2S)	113.9(2)

Table 7.12. Atomic coordinates (x 10^4) and equivalent isotropic displacement coefficients ($Å^2$ x 10^3) for **137b** with e.s.d.'s in parentheses.

atom	x	y	z	U_{eq}[a]
C(1)	5880(7)	2490(4)	4117(5)	23(3)
C(2)	4983(7)	2222(4)	4869(6)	26(3)
C(3)	3876(7)	2792(4)	4785(5)	24(3)
C(4)	2621(7)	2489(4)	4720(6)	29(3)
C(5)	1963(7)	2545(5)	5508(6)	40(3)
C(6)	2430(7)	2898(4)	6501(6)	35(3)
C(7)	3557(7)	3183(4)	6678(5)	24(3)
C(8)	4383(7)	3161(4)	5843(5)	19(3)
C(9)	5485(7)	2584(4)	5925(5)	21(3)
C(10)	6620(7)	3041(4)	5658(5)	23(3)
C(11)	6020(7)	3734(4)	5048(5)	22(3)
C(12)	4858(6)	3956(4)	5516(5)	20(3)
O(12)	4949(4)	4518(3)	6290(3)	26(2)
N(13)	4042(5)	4177(3)	4562(4)	23(2)
C(14)	4147(7)	3438(4)	4004(5)	25(3)
C(15)	5521(6)	3351(4)	3977(5)	23(3)
C(16)	7086(6)	2528(5)	4823(5)	30(3)
C(1')	-1579(7)	3840(4)	1984(5)	29(3)
C(2')	-674(7)	4329(4)	1420(5)	26(3)
C(3')	-529(7)	5140(4)	1954(5)	24(3)
C(4')	-550(8)	5850(5)	1317(5)	30(3)
C(5')	453(8)	6268(5)	1271(6)	36(4)
C(6')	1628(8)	6050(5)	1800(6)	36(4)
C(7')	1763(7)	5409(5)	2384(5)	26(3)
C(8')	715(6)	4897(4)	2515(5)	22(3)
C(9')	586(7)	4089(4)	1996(6)	30(3)
C(10')	244(7)	3483(4)	2807(5)	26(3)
C(11')	-271(6)	4024(4)	3596(5)	20(3)
C(12')	435(7)	4792(5)	3647(5)	23(3)
O(12')	1438(4)	4855(3)	4375(3)	27(2)
N(13')	-543(5)	5370(3)	3774(4)	25(2)
C(14')	-1351(7)	5138(4)	2844(5)	24(3)
C(15')	-1537(7)	4269(4)	3028(5)	24(3)
C(16')	-888(7)	3085(4)	2255(6)	38(3)
C(1B)[b]	3789(8)	-29(5)	5067(9)	57(4)
C(2B)[b]	4575(10)	-63(5)	5956(7)	55(4)
C(3B)[b]	5793(9)	-36(5)	5869(8)	55(4)

[a] Equivalent isotropic U defined as one third of the U_{ij} tensor. [b] Benzene solvate.

Table 7.13. Bond lengths (Å) and angles (°) for **137b** with e.s.d.'s in parentheses.

molecule	A	B		A	B
C(1)-C(2)	1.544 (11)	1.558(11)	C(1)-C(15)	1.544 (10)	1.545(10)
C(1)-C(16)	1.544 (9)	1.533(11)	C(2)-C(3)	1.571 (11)	1.562(11)
C(2)-C(9)	1.558 (10)	1.574(10)	C(3)-C(4)	1.487 (11)	1.478(11)
C(3)-C(8)	1.567 (10)	1.553(10)	C(3)-C(14)	1.561 (11)	1.555(10)
C(4)-C(5)	1.329 (12)	1.336(12)	C(5)-C(6)	1.472 (11)	1.461(12)
C(6)-C(7)	1.345 (11)	1.340(11)	C(7)-C(8)	1.500 (11)	1.489(11)
C(8)-C(9)	1.575 (10)	1.548(11)	C(8)-C(12)	1.546 (11)	1.552(10)
C(9)-C(10)	1.561 (10)	1.562(11)	C(10)-C(11)	1.546 (10)	1.545(11)
C(10)-C(16)	1.535 (10)	1.542(11)	C(11)-C(12)	1.538 (11)	1.537(11)
C(11)-C(15)	1.589 (10)	1.577(10)	C(12)-O(12)	1.393 (9)	1.388(8)
C(12)-N(13)	1.506 (9)	1.498(10)	N(13)-C(14)	1.478 (10)	1.482(8)
C(14)-C(15)	1.543 (10)	1.535(11)			
C(1B)-C(2B)	1.376 (14)		C(1B)-C(3BA)	1.356 (16)	
C(2B)-C(3B)	1.375 (15)		C(3B)-C(1BA)	1.356 (16)	

C(2)-C(1)-C(15)	100.7(6)	101.4(6)	C(2)-C(1)-C(16)	102.5(5)	103.4(6)
C(15)-C(1)-C(16)	103.1(6)	103.7(6)	C(1)-C(2)-C(3)	109.1(6)	108.3(6)
C(1)-C(2)-C(9)	104.2(6)	102.9(6)	C(3)-C(2)-C(9)	90.8(5)	88.8(5)
C(2)-C(3)-C(4)	120.7(6)	119.8(6)	C(2)-C(3)-C(8)	89.3(5)	90.7(6)
C(4)-C(3)-C(8)	116.1(6)	116.5(6)	C(2)-C(3)-C(14)	106.6(6)	106.9(6)
C(4)-C(3)-C(14)	117.5(6)	116.5(6)	C(8)-C(3)-C(14)	101.9(6)	102.5(5)
C(3)-C(4)-C(5)	121.7(7)	120.6(7)	C(4)-C(5)-C(6)	122.5(7)	123.5(8)
C(5)-C(6)-C(7)	122.4(7)	121.2(8)	C(6)-C(7)-C(8)	120.2(6)	120.8(7)
C(3)-C(8)-C(7)	117.2(6)	117.2(6)	C(3)-C(8)-C(9)	90.4(5)	90.1(5)
C(7)-C(8)-C(9)	120.2(6)	121.3(6)	C(3)-C(8)-C(12)	102.6(5)	102.5(6)
C(7)-C(8)-C(12)	115.7(6)	114.8(6)	C(9)-C(8)-C(12)	106.9(6)	107.0(6)
C(2)-C(9)-C(8)	89.5(5)	90.4(6)	C(2)-C(9)-C(10)	103.1(6)	103.1(6)
C(8)-C(9)-C(10)	108.1(6)	108.9(6)	C(9)-C(10)-C(11)	100.9(6)	100.5(6)
C(9)-C(10)-C(16)	102.2(6)	103.3(6)	C(11)-C(10)-C(16)	104.0(6)	103.5(6)
C(10)-C(11)-C(12)	109.0(6)	108.9(6)	C(10)-C(11)-C(15)	102.7(6)	103.2(6)
C(12)-C(11)-C(15)	102.8(5)	102.6(6)	C(8)-C(12)-C(11)	102.5(6)	102.3(6)
C(8)-C(12)-O(12)	114.6(6)	114.2(6)	C(11)-C(12)-O(12)	117.5(6)	117.9(6)
C(8)-C(12)-N(13)	105.0(5)	104.5(6)	C(11)-C(12)-N(13)	101.2(5)	101.6(6)
O(12)-C(12)-N(13)	114.2(6)	114.4(6)	C(12)-N(13)-C(14)	96.6(5)	96.7(5)
C(3)-C(14)-N(13)	105.3(6)	104.7(6)	C(3)-C(14)-C(15)	102.1(6)	102.6(6)
N(13)-C(14)-C(15)	103.1(6)	102.4(5)	C(1)-C(15)-C(11)	103.5(5)	102.9(6)
C(1)-C(15)-C(14)	109.6(6)	108.8(6)	C(11)-C(15)-C(14)	101.1(6)	101.8(6)
C(1)-C(16)-C(10)	96.1(5)	95.5(6)			
C(2B)-C(1B)-C(3BA)	120.7(9)		C(1B)-C(2B)-C(3B)	118.3(9)	
C(2B)-C(3B)-C(1BA)	121.1(9)				

Figure 7.1. Perspective view and atom labelling of the X-ray structure of **65**.

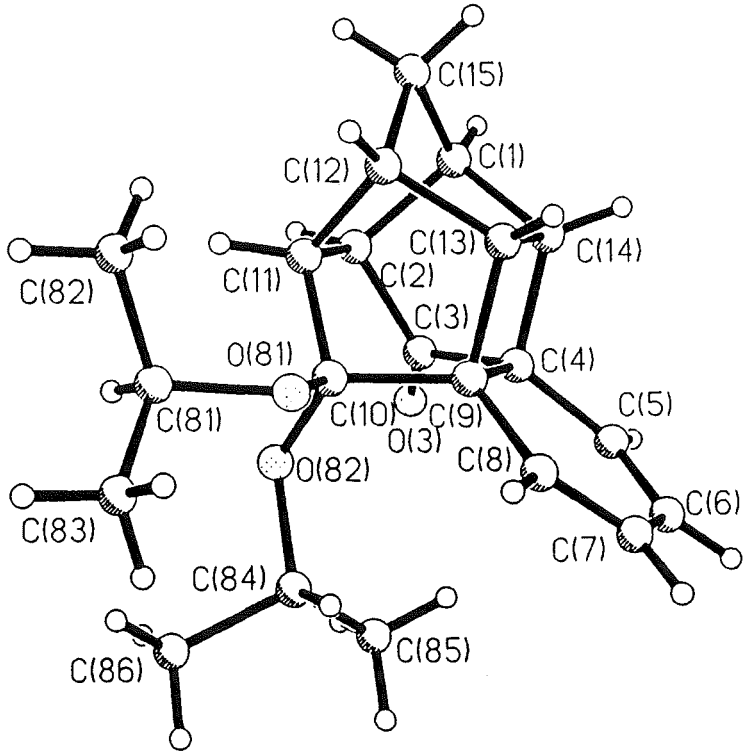


Figure 7.2. Perspective view and atom labelling of the X-ray structure of **99**.

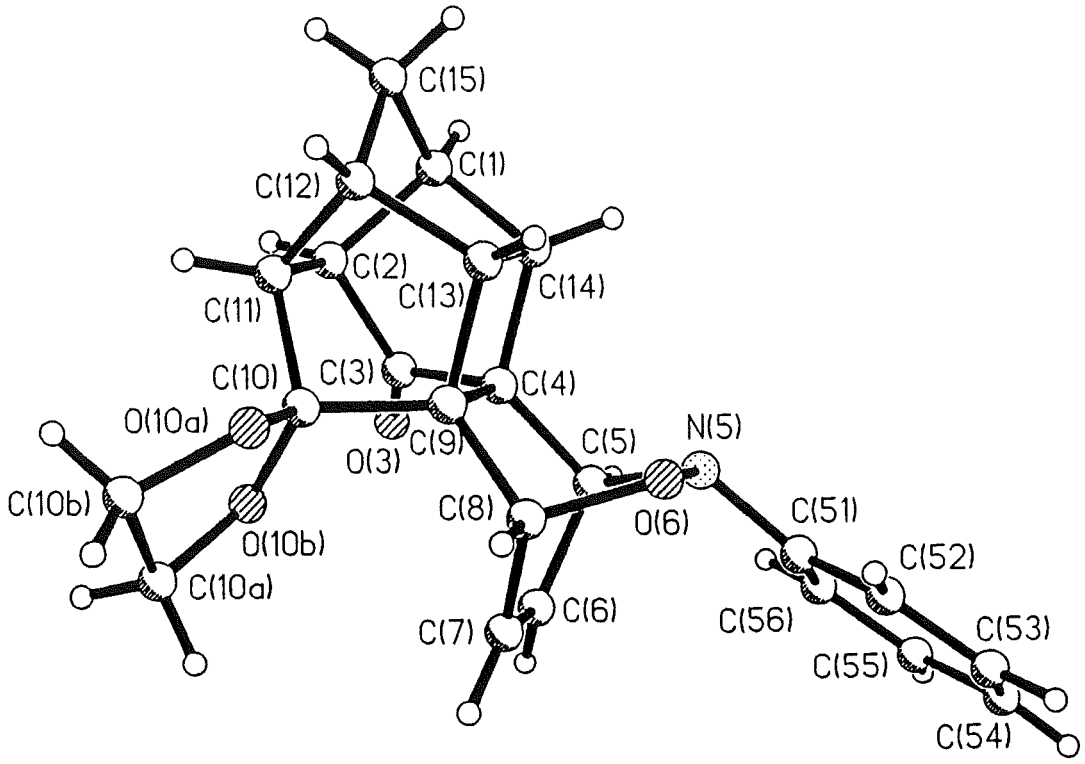


Figure 7.3. Perspective view and atom labelling of the X-ray structure of **117**.

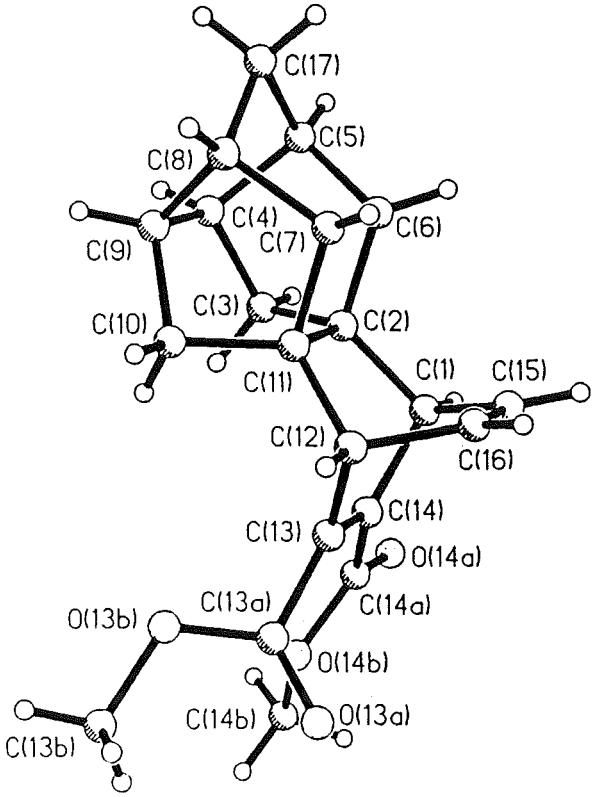


Figure 7.4. Perspective view and atom labelling of the X-ray structure of **119**

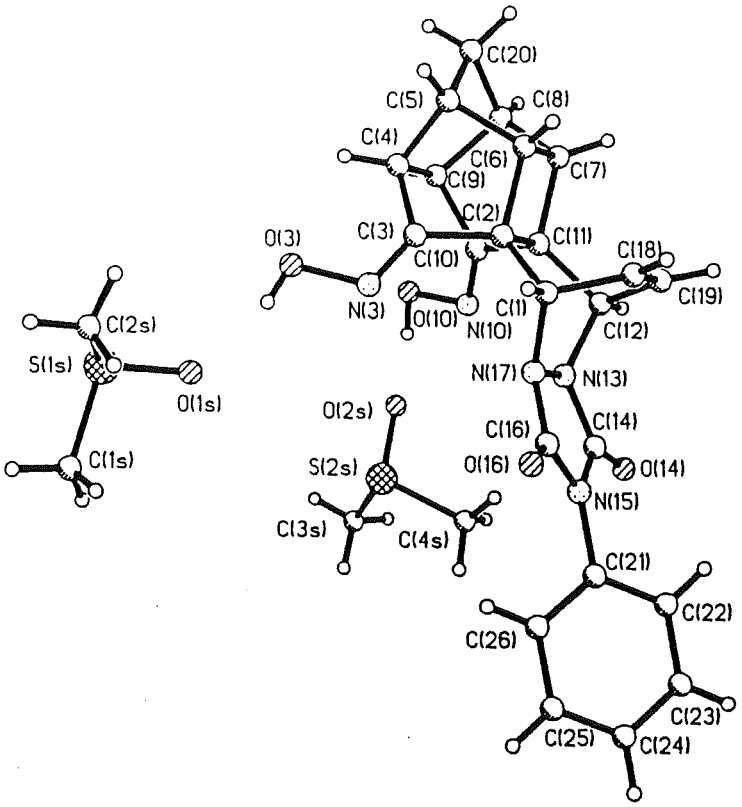


Figure 7.5. Perspective view and atom labelling of the X-ray structure of **134a**.

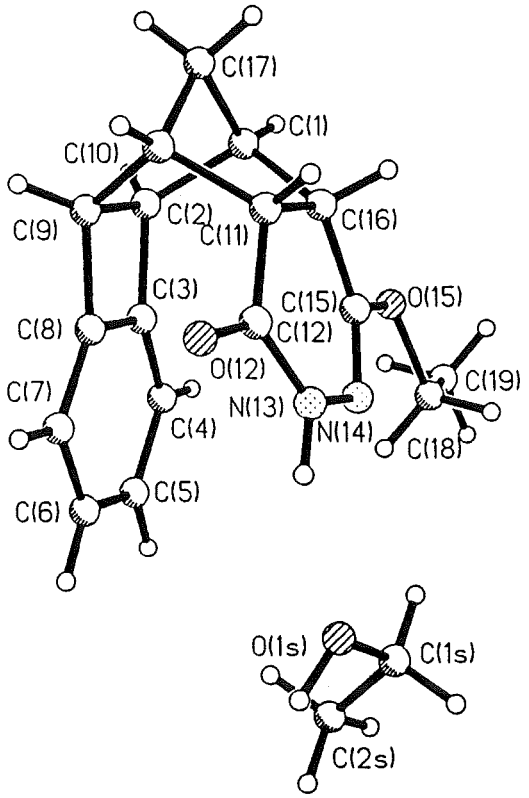
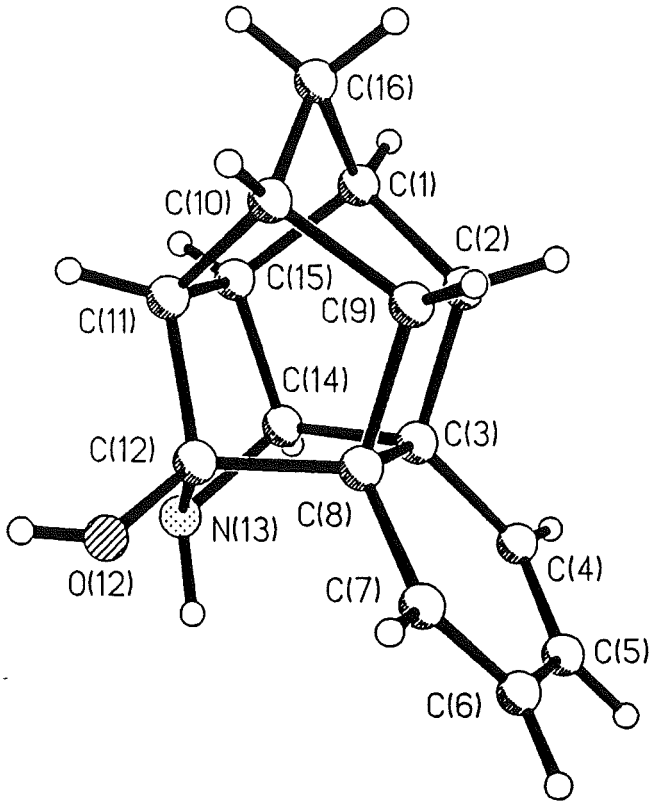


Figure 7.6. Perspective view and atom labelling of the X-ray structure of **137b**.



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